NEW AND EMERGING METHODS
Zhongjian Ju, et al.: CyberKnife SBRT dose gradient

Dose fall-off during the treatment of thoracic spine metastasis with CyberKnife stereotactic body radiation therapy (SBRT)

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ABSTRACT
CyberKnife stereotactic body radiation therapy (SBRT) is becoming increasingly used for cancer treatment and, to maximize its clinical application, it is important to define the dosimetric characteristics, optimal dose and fractionation regimens. The aim of this study was to evaluate the dose fall-off in two fractionated regimens of CyberKnife SBRT during the treatment of thoracic spinal metastasis. Patients with spinal metastasis involving a vertebra and pedicle were treated with 40 Gy in 5 fractions (n = 4), and patients with spinal metastasis involving only a vertebra received 33 Gy in 3 fractions (n = 4). A new approach was used to measure absolute dose fall-off distance, relative dose fall-off distance, and the dose fall-off per unit distance along four reference directions in the axial plane. Patients treated with 33 Gy/3 fractions had a greater absolute dose fall-off distance in direction 1 (from the point with maximum dose [Dmax] towards the spinal cord) and direction 3 (the opposite of the direction 1), a greater relative dose fall-off distance in direction 3, and a lower dose fall-off per unit distance in direction 1 and 3 compared to patients treated with 40 Gy/5 fractions (all \( p < 0.05 \)). Overall, the dose fall-off towards the spinal cord is rapid during the treatment of thoracic spinal metastasis with CyberKnife SBRT, which allows a higher dose of radiation to be delivered to the tumor and, at the same time, better protection of the spinal cord.

KEY WORDS: CyberKnife; dosage; radiation; stereotactic body radiation therapy; SBRT thoracic spine metastasis; dose gradient
INTRODUCTION

Bone metastases can occur in up to 48% of patients with stage IV lung cancer [1, 2], as well as with other common primary solid tumors such as breast cancer, prostate cancer [3], and renal carcinoma [4]. Symptomatic spinal metastases may develop in up to 10% of cancer patients [5]. Bone metastases often lead to increased bone resorption, which can trigger fractures, spinal cord compression, and severe bone and neuropathic pain [5-7]. Metastatic spinal cord compression is a common complication of cancer, with back pain a common symptom, and can present as an oncologic emergency [8]. Conventional radiotherapy is delivered in 5 to 20 fractions over 5 to 20 days, and can provide pain relief in approximately 70% to 80% of patients with spinal metastasis within 3 months [9,10], but it is not used to treat recurrent spinal metastases. Stereotactic body radiation therapy (SBRT) has become a prominent treatment approach for spinal metastases, and provides a rapid pain relief (24-72 hours) in 84% to 90% of patients that lasts for 1 year or longer [4, 5, 10-12]. It is especially useful for patients who are not candidates for surgical removal [4].

The CyberKnife system (Accuracy, Inc., Sunnyvale, CA), a stereotactic radiosurgery platform, provides real-time image tracking linked to internal anatomical structures (e.g., skull) to monitor the position of the lesion, alignment of the independent beams to the treatment target, and relatively precise delivery of radiation of 100 to 150 independent beams for a pre-specified distance to avoid or reduce exposure to organs-at-risk such as the radiosensitive spinal cord [10]. Its robotic arm has six axes of freedom, and is coupled with two ceiling mounted X-ray cameras for monitoring target position [10]. The CyberKnife system has a unique Xsight spine-tracking mode, which allows real-time tracking of changes in the target area of the spine, and controls position error within a range of 0.53±0.16 mm during treatment [13]. Because the CyberKnife provides precise delivery of radiation, a
higher dose in a single fraction can be given while avoiding radiation to the spinal cord. A higher dose in one fraction is preferred, because a higher dose has a greater radiobiological effect with respect to reducing the size of a tumor, and thus provides better pain control compared with the routine radiotherapy [5, 10, 13].

Dosimetric characterization of the CyberKnife for spinal metastases typically ranges retrospectively from 8 Gy to 24 Gy for a single dose, and from 18 Gy to 36 Gy for multiple fractions [14]. The dose fall-off gradient can be used for evaluating the quality of the treatment plan, and selecting different treatment methods [15].

The purpose of this study was to investigate the dose fall-off gradient pattern of the CyberKnife when used to treat thoracic spine metastasis in 2 different treatment planning approaches (40 Gy/5 F and 33 Gy/3 F). The results can provide information to clinicians when they need to make a quick judgement about whether the dose accumulated in the spinal cord surpasses the dose limit. Alternatively, if metastases are very close to the spinal cord, the results can help the clinician evaluate the potential trade-off between therapeutic effect and protection of the spinal cord.
MATERIALS AND METHODS

Patients

Patients with a single spinal metastasis who were expected to survive more than 6 months admitted to our hospital from November 2011 and August 2013 were recruited for this study. Inclusion criteria were a Karnofsky Performance Status (KPS) score greater than 65 and TNM stage IV at the time of diagnosis. Patients in whom bone metastases were found after surgery were excluded.

Ethical approval and consent to participate

This study was approved by the Institutional Review Board of Hainan Branch of Chinese PLA General Hospital, and all patients provided written informed consent.

Scanning and definition of the target area and important organs

The patient was placed in the supine position and fixed with vacuum pads. Computed tomography (CT) locating was performed with a Philips Brilliance CT Big Bore (Netherlands) CT scanner. The slice thickness was 1.5 mm. Data were transferred to a MultiPlan 4.0.2 system via DICOM to outline the target area and organs-at-risk.

The target area and organs-at-risk were outlined on the CT simulation images by medical physicists, as previously described [16]. The target areas included gross tumor volume (GTV) and planning target volume (PTV). Tumor area was first identified on diagnostic magnetic resonance imaging (MRI) or positron emission tomography (PET)-CT images, and GTV was then outlined on the CT simulation images. The PTV was defined with 3 mm margins beyond the GTV in all dimensions. Because the metastases of all patients were located in the thoracic region, the organ-at-risk was the region of the spinal cord exposed on the CT bone window.

Dmax, the point with maximum dose, was calculated by the planning system for each patient. The 70% isodose line, instead of the median (80%) isodose line (70-94%), was used to cover the PTV in accordance with the characteristics of the CyberKnife system.
Treatment plan design and dosing

The target area and organs-at-risk were outlined using the MultiPlan 4.0.2 in the CyberKnife system, and a SBRT plan was designed for each patient. Two collimators were used, and the dose rate was 800 cGy/min. The extent of target-area coverage was increased as much as possible, while maintaining the dose limits for normal organs. Each treatment plan guaranteed that 70% of the isodose line covered more than 85% of the target volume. The dose distribution is shown in Figure 1.

The collimator size was selected according to the target volume and clinical experience, and was thus different in each patient. In general, a collimator size of 1/3 and 2/3 of maximal diameter will achieve the best results.

The selection of treatment dose was based on the extent of metastasis. A dose of 40 Gy was administered in 5 fractions to the PTV of patients with vertebral and pedicle metastasis. The dose limit for the spinal cord in the 5-fraction treatment mode was $D_{\text{max}} < 30$ Gy, $V_{22.5} < 0.25$ ml and $V_{13.5} < 1.2$ ml [17]. A dose of 33 Gy was given in 3 fractions to the PTV of patients with single vertebral metastasis. These patients had primary lung or nasopharyngeal cancer, and a distance of < 5 mm between the GTV and spinal cord. Dose limit for the spinal cord in the 3-fraction treatment mode was $D_{\text{max}} < 22$ Gy, $V_{18} < 0.25$ ml and $V_{11.1} < 1.2$ ml [17].

A number of methods were used to assure target coverage and limitation of spinal cord dose: several cold help regions were defined in the target area to improve the coverage; 8 shells with different diameters and different dose limitations were defined around the tumor to control the low dose area; 3-5 hot help structures were defined in the spinal cord area to reduce the spinal cord dose.

Measurement of parameters related to the dose gradient

The straight line beginning at $D_{\text{max}}$ extending towards spinal canal center in the axial plane was defined as direction 1 (Figure 2). The other 3 directions evenly spaced 90° apart in the
axial plane were designated as direction 2, 3, and 4 in a clockwise order (Figure 2). For measurement of absolute dose fall-off distance, the distance between 2 adjacent points of dose fall-off of 100 cGy was measured between the starting point of the prescribed dose to the point of its 30% dose (Figure 3). The relative dose fall-off distance was defined as the distance between 2 adjacent points of dose fall-off 5% from Dmax to the point of 30% prescribed dose (Figure 4). For measurement of the dose fall-off per unit distance, the changes in dose were measured every 1 mm from Dmax to a point 30 mm away (Figure 5).

**Statistical analysis**

Continuous variables were expressed as mean ± standard deviation. Post-hoc pairwise comparisons were performed by Wilcoxon signed rank test with a significance level of 0.05. The Friedman test was used to compare differences between different directions in the 2 treatment groups. Comparisons of within group differences in different directions were performed by Mann-Whitney test. All statistical assessments were 2-sided, and evaluated at the 0.05 level of significance. Statistical analyses were performed with IBM SPSS statistical software version 22 for Windows (IBM Corp., Armonk, New York, USA).
RESULTS

Eight patients, 6 males and 2 females with a mean age of 58.4 years, with metastases in the thoracic spine were included in the study (Table 1).

Four patients had metastases extended into the vertebra and the pedicle (40 Gy/5 F group). The median PTV volume was 22.99 cc (range, 4.58-28.61 cc), median isodose value was 69% (range, 65-70%), and median coverage was 91.95% (range, 74.61-94.9%).

Four patients had metastases extended only into the vertebra (33 Gy/3 F group). The median PTV volume was 12.42 cc (range, 7.4-27.3 cc), median isodose value was 70% (range, 70-80%), and median coverage was 90.52% (range, 88.6-96.2%).

Absolute dose fall-off distance

In the 40 Gy/5 F group, the average absolute fall-off distances in the 4 directions were significantly different (0.208, 0.720, 0.661, and 0.811 mm/100 cGy, p < 0.001) (Table 2). The absolute dose fall-off distance in direction 2, 3, and 4 was significantly greater than in direction 1 (all, p < 0.05). The absolute dose fall-off distance in direction 4 was significantly greater than in direction 2 and 3 (both, p < 0.05), but that of direction 3 was significantly less than in direction 2 (p < 0.05).

In the 33 Gy/3 F group, the average absolute fall-off distances in the 4 directions were significantly different (0.287, 0.670, 1.018 and 0.721 mm/100 cGy, p < 0.001) (Table 2). The average dose fall-off distance in direction 2, 3, and 4 was significantly greater than in direction 1 (all, p < 0.05). The average dose fall-off distance in direction 3 and 4 was significantly greater than in direction 2 (both, p < 0.05), but the dose fall-off distance in direction 4 was significantly lesser than that of direction 3 (p < 0.05). In addition, the absolute dose fall-off distances in directions 1 and 3 of the 33 Gy/3 F group were significantly greater than in the corresponding directions of the 40 Gy/5 F group (both, p < 0.05).
Relative dose fall-off distance

In the 40 Gy/5 F group, there were significant differences in the relative dose fall-off distance in directions 1, 2, 3, and 4 (0.868, 1.477, 1.565, and 1.699 mm/5% D<sub>max</sub>, p < 0.001; Table 3). The relative dose fall-off distances in direction 2, 3, and 4 was significantly greater than that in direction 1 (all, p < 0.05), and the relative dose fall-off distance in direction 4 was significantly greater than that in direction 3 (p < 0.05).

In the 33 Gy/3 F group, there were significant differences in the relative dose fall-off distance in direction 1, 2, 3, and 4 (0.689, 1.534, 2.364, and 1.603 mm/5 % D<sub>max</sub>, p < 0.001; Table 3). The relative dose fall-off distance in direction 2, 3, and 4 was significantly greater than in direction 1 (all, p < 0.05), and it was significantly greater in direction 3 than direction 2 (p < 0.05). However, the relative dose fall-off distance in direction 4 was significantly less than in direction 3 (p < 0.05). In addition, the relative dose fall-off distance of the 33 Gy/3 F group was significantly greater in direction 3 than in direction 3 in the 40 Gy/5 F group (p < 0.05).

Dose fall-off per unit distance

In the 40 Gy/5 F group, there were significant differences in the dose fall-off per unit distance in the 4 directions (353.628, 221.955, 243.669, and 196.428 cGy/mm, p < 0.001; Table 4). The dose fall-off per unit distance in direction 2, 3, and 4 was significantly lower than in direction 1 (all, p < 0.05). The dose fall-off per unit distance in direction 3 was significantly higher than in direction 2 (p < 0.05) and direction 4 (p < 0.05).

In the 33 Gy/3 F group, there were significant differences in the dose fall-off per unit distance in the 4 directions (266.269, 191.784, 148.6 and 174.945 cGy/mm, p < 0.001; Table 4). The dose fall-off per unit distance in direction 2, 3 and 4 was significantly lower than in direction 1 (all, p < 0.05). The dose fall-off per unit distance was greatest in direction 1, followed by direction 2, direction 4, and direction 3 (p < 0.05). In addition, the 40 Gy/5 F group had a significantly greater dose fall-off per unit distance in direction 1 and 3 than the 33 Gy/3 F
DISCUSSION

This study of CyberKnife treatment of spinal metastasis showed that a dose of 33 Gy/3 F has a greater absolute dose fall-off distance in direction 1 and 3, a greater relative dose fall-off distance in direction 3, and a lower dose fall-off per unit distance in direction 1 and 3 as compared to 40 Gy/5 F. Generally, the dose fall-off rate in the direction of the spinal cord was significantly steeper in the 40 Gy group than in the 33 Gy group. A possible reason is that the target area in the 33 Gy group simply included the vertebral body, and it was easy to reach the spinal cord dose limit. In comparison, the 40 Gy group included the vertebral body and the pedicle. Therefore, in the 33 Gy group, the dose distribution interval was relatively loose, and the dose fall-off gradient was relatively slow. Both dosing patterns studied are commonly used in clinical practice, and the results may assist in determining dose selection for individual patients.

The selection of appropriate directions for the investigation of dose-fall was done after careful consideration. Previous studies usually used common anatomical directions, such as anterior to the target volume, or posterior to the target volume, to investigate the dose fall-off [18]. However, few studies have investigated the dose-fall of SBRT in the case of thoracic spine metastasis, and the previous methods used for intensity-modulated radiation therapy (IMRT) are not applicable. Since the spinal cord should be protected, and is also close to the target lesion, the dose must be strictly controlled. Additionally, in the case where PTV is at some distance from critical normal tissues, the selection of reference direction may not significantly bias the results. However, in the present study, PTV was close to the spinal cord, and a difference in starting point of even only 1 mm will significantly impact the outcome. As shown in Figure 4, the direction from Dmax to the spinal canal center is vertical to the isodose line; if the direction is selected from the tumor center (black arrow in Figure 4), the
distance is shortened, and the dose-fall rate increases, which is incorrect. Thus, in this study we tried to use the newer standards, defining the major reference direction (direction 1) from Dmax to the spinal canal center and measuring the dose-fall along the direction. We believe that the distance between different isodose lines and Dmax may better reflect the actual dose-fall.

In this study, the prescribed dose was based on the extent of tumor invasion. Due to the radiobiological effect on a tumor, a higher dose in one fraction can bring about a more rapid therapeutic effect. Additionally, different numbers of fractions render different dose limits for the spinal cord. Therefore, when the spinal cord is well-protected, we prefer to use a higher dose in one fraction, e.g., 11 Gy × 3 fractions (3-fraction treatment mode: Dmax < 22 Gy, V18 < 0.25 ml, and V11.1 < 1.2 ml). When a tumor invades the pedicles, PTV becomes larger. A larger PTV makes the treatment planning more complicated. In order to provide better protection of the spinal cord, a lowered dose is adopted, e.g., 8 Gy × 5 fractions (5-fraction treatment mode: Dmax < 30 Gy, V22.5 < 0.25 ml, and V13.5 < 1.2 ml).

It should be mentioned that contouring the spinal cord only on CT simulation images does not provide the best possible accuracy. MRI simulation images can definitely provide a more accurate contour of the spinal cord. But for patients with spine metastasis, the tremendous pain usually makes waiting 2 weeks for an MRI simulation scan based on our hospital’s schedule intolerable. Therefore, we administer radiotherapy as soon as possible based on CT simulation images to offer pain relief. Because the spinal cord cannot be accurately delineated on the CT images, we include the space in the contour of the dura sac as an organ at risk. It can be seen in the Figures 1-5 that the green contours define the region of organ at risk, including the spinal cord. In the study, we adopted a more conservative approach to calculate the dose accumulated in the spinal cord.

There are a number of limitations to this study. First, the study only included 8 patients, and 2
different doses were used. Second, choosing Dmax as the center point, and measuring the dose gradient along the reference direction between Dmax and the spinal cord did not perfectly indicate how fast the dose could fall off because the gradient in this reference direction did not always represent the direction of steepest descent of the dose. Third, because the prescribed dose in the tumor was normalized to 70% during design of the treatment plan, some data inside the target area had to be discarded during statistical analysis. Forth, we did not compare CyberKnife dose fall-off with other treatment machines. Fifth, unlike IMRT, using SBRT for treatment planning doesn’t require that the dose distribution meet HI criteria. Therefore, we didn’t consider providing HI for comparison.
CONCLUSION

In conclusion, a new approach to measure the dose fall-off gradient was presented when using radiosurgery to treat a spine metastasis. Because of its fast dose fall off, CyberKnife SBRT provides protection of the spinal cord when the spinal cord is extremely close to the PTV. The information provided from this study can serve as a good reference for medical physicists when they need to optimize a treatment plan in similar cases.

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DECLARATION OF INTERESTS

The authors declare no conflict of interests.
REFERENCES


FIGURES AND TABLES

Figure 1

FIGURE 1. Dose distribution of the treatment plan and dose-volume histogram.
FIGURE 2. Diagram of the reference directions. The red point denotes the Dmax. The green point stand denotes the center of spinal canal. The outer red line denotes the contour of PTV. The inner red line denotes the contour of GTV. The green line denotes the contour of spinal canal. The blue arrows denote the direction 1, 2, 3, and 4.
FIGURE 3. Measurement of absolute dose fall-of distance. The double-ended red arrows indicate the range of measurements. The red point denotes the Dmax. The blue arrows denote the direction 1, 2, 3 and 4.
FIGURE 4. Measurement of relative dose fall-off distance. The double-ended red arrows indicate the range of measurements. The red point denotes the Dmax. The blue arrows denote the direction 1, 2, 3 and 4. The black point denotes the center of tumor. The black arrow denotes the direction from the center of tumor to the center of spinal canal.
FIGURE 5. Measurement of dose fall-off per unit distance. The double-ended red arrows indicate the range of measurements. The red point denote the Dmax. The blue arrows the direction 1, 2, 3 and 4.
<table>
<thead>
<tr>
<th></th>
<th>Total (N=8)</th>
<th>Treatment</th>
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<tr>
<td></td>
<td></td>
<td>40 Gy/5 F (n=4)</td>
</tr>
<tr>
<td>Age</td>
<td>58.4±11.5</td>
<td>66.8±9.5</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>2 (25.0)</td>
<td>1 (25.0)</td>
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<tr>
<td>Male</td>
<td>6 (75.0)</td>
<td>3 (75.0)</td>
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<tr>
<td>KPS</td>
<td>76.3±7.9</td>
<td>70.0±5.8</td>
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</tbody>
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KPS: Karnofsky Performance Status.
Continuous variables were shown as mean ± standard deviation; categorical variable as number (percentage).
**TABLE 2. Absolute dose fall-off distance**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Absolute dose fall-off distance (mm/100 cGy)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Direction 1</td>
<td>Direction 2</td>
</tr>
<tr>
<td>40 Gy/5 F</td>
<td>0.208±0.086</td>
<td>0.720±0.882	extsuperscript{a}</td>
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<tr>
<td>33 Gy/3 F</td>
<td>0.287±0.078	extsuperscript{†}</td>
<td>0.670±0.420	extsuperscript{a}</td>
</tr>
</tbody>
</table>

*Significant difference among the 4 directions, p < 0.001.

	extsuperscript{a} Significant difference from direction 1, p < 0.05.

	extsuperscript{b} Significant difference from direction 2, p < 0.05.

	extsuperscript{c} Significant difference from direction 3, p < 0.05.

	extsuperscript{†} Significant difference between 40 Gy/5 F and 33 Gy/3 F, p < 0.05.
**TABLE 3. Relative dose fall-off distance**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Direction 1</th>
<th>Direction 2</th>
<th>Direction 3</th>
<th>Direction 4</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 Gy/5 F</td>
<td>0.868±0.602</td>
<td>1.477±0.822</td>
<td>1.565±1.585</td>
<td>1.699±0.904</td>
<td>&lt;0.001*</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>33 Gy/3 F</td>
<td>0.689±0.161</td>
<td>1.534±1.024</td>
<td>2.364±1.220</td>
<td>1.603±0.628</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*Significant difference among the 4 directions, p < 0.001;  
* Significant difference from direction 1, p < 0.05.  
* Significant difference from direction 2, p < 0.05.  
* Significant difference from direction 3, p < 0.05.  
† Significant difference between 40 Gy/5 F and 33 Gy/3 F, p < 0.05.
## TABLE 4. Dose fall-off per unit distance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose fall-off per unit distance (cGy/mm)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Direction 1</td>
<td>Direction 2</td>
</tr>
<tr>
<td>40 Gy/5 F</td>
<td>353.628±160.48</td>
<td>211.955±86.628</td>
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<tr>
<td>33 Gy/3 F</td>
<td>266.269±94.408(^†)</td>
<td>191.784±61.373</td>
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</table>

*Significant difference among the 4 directions, p < 0.001;
\(^a\) Significant difference from direction 1, p < 0.05.
\(^b\) Significant difference from direction 2, p < 0.05.
\(^c\) Significant difference from direction 3, p < 0.05.
\(^†\) Significant difference between 40 Gy/5 F and 33 Gy/3 F, p < 0.05.