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Robotic Image-Guided Radiosurgery for the Treatment of Neoplastic Vertebral Pain: A Review of the Current Literature

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Abstract

Metastatic spinal lesions are a common event in cancer patients. Spinal metastases usually involve the vertebral bodies and are characterized by severe pain. Surgical treatment, as a consequence of its high invasivity, is rarely offered to patients with metastatic disease and expected limited life span. Spinal radiosurgery provides high rates of pain and local growth control in association with limited risk of neurological complications. The use of radiosurgery to treat spinal lesions has been strongly facilitated by the development of image-guided robotic radiosurgery, a technique able to deliver stereotactic irradiation to intra- and extracranial targets. Despite the exponential increase of treatments delivered to the spine using this novel approach and the growing number of papers reporting the outcomes of spine radiosurgery in terms of local growth control and analgesia following treatment of patients with metastatic and benign lesions of the spine, the awareness of the general medical public to the use of this technique remains limited. This paper aims to review the role of radiosurgery in the treatment of vertebral metastases and benign tumors and its efficacy in terms of pain and local growth control.

Categories: Radiation Oncology, Neurosurgery
Keywords: image-guided, robotic, cancer, metastatic, pain, radiosurgery, spine, palliation

Introduction And Background

The skeletal system is the third most frequent site of metastases after lung and liver, and the spine is the most common site of skeletal metastases [1]. Spinal metastases in patients with advanced cancer can cause significant morbidity, with pain and/or neurological deficits adversely affecting the patients' survival and quality of life. Due to increased life expectancy of cancer patients, a rise in incidence of vertebral metastases has recently been observed and management of such patients has become a major neurosurgical issue.

Pain relief in patients with metastatic or primary spinal lesions is usually achieved with steroidal or non-steroidal anti-inflammatories [2] and opioids, often in combination with external beam radiation [3], surgery [4], and, in some cases, chemotherapy [3]. Steroids are effective in reducing the spinal cord edema temporarily and thus allowing radiotherapy or surgery of the lesion.

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Surgery is the treatment of choice for metastases that require decompression and vertebral stabilization. A simple laminectomy should be reserved for very rare cases, such as when only the spinous process or lamina is involved, or in the case of a purely epidural lesion. If surgery is to be performed, the anterior column needs to be attended to through several surgical approaches, and even a posterior approach should not exclude accessing the vertebral bodies and reconstruction of the anterior column. Advanced surgery eliminates instability of the spine, relieves neurologic compromise and pain, and provides histologic material for pathologic diagnosis. Nevertheless, due to potential complications, life expectancy and general condition of the patient ultimately determines the feasibility of this option. Radiotherapy is also a very efficient option for pain relief, neurological function preservation or recovery, and control of tumor growth [5]. Although both single- and multiple-fraction radiotherapy regimens have been demonstrated to be effective in different instances [5-7], advancements that can provide a boost to the therapeutic efficacy of radiation therapy are still desirable.

Benign spinal tumors, including schwannomas, meningiomas, chondromas, and neufibromas are usually treated with surgery [8-9]. Local or radicular pain, along with radicular or myelopathic weakness, axial sensory loss, and bladder paresis, can manifest as symptoms of benign spinal tumors [10]. Radiosurgery is the treatment of choice for selected cases of benign brain tumors [11-12].

Progress in radiation therapy of spinal tumors is dependent on development of new technologies to improve tumor targeting, increase therapeutic dose, aid normal tissue sparing, and improve dose conformality. All these can be achieved with radiosurgery. Radiosurgery is defined as the delivery, in a single or few fractions, of a concentrated dose of radiation to inactivate or eradicate a target, with a steep dose fall-off outside the treatment volume [13]. The technique was first developed in the late 1940s by the Swedish neurosurgeon, Lars Leksell [14]. The required high spatial accuracy of dose delivery to intracranial targets was achieved with the use of a rigid frame designed by Leksell. The stereotactic frame, anchored to the patient's skull, provides external reference points for target localization, and is still in widespread use. Initial attempts at spinal radiosurgery also involved a stereotactic frame that was fixed to the spine with bone screws applied under general anesthesia [15]. This frame was invasive and uncomfortable for the patient and tended to introduce image artifacts in the CT. The development of a more flexible and less painful approach called image-guided, or frameless, radiosurgery has allowed the principles of intracranial radiosurgery to be applied to the treatment of spinal lesions [16-17].

Three image-guided linear accelerator (LINAC)-based devices are currently used to deliver spinal radiosurgery [18]: the Novalis Tx™ (BrainLAB AG, Feldkirchen, Germany), an intensity-modulated gantry-based system, which takes advantage of external infrared light-emitting diodes placed on the patient's body and couch adjustment based on optical tracking combined with X-ray imaging; TomoTherapy® Hi-Art® (TomoTherapy Incorporated, Madison, WI, USA), using CT technology for image guidance, however, is not yet equipped with a system that would allow intrafractional corrections without treatment interruption; and the CyberKnife® (Accuray Incorporated, Sunnyvale, CA, USA), a device that uses a robotic arm to position a compact LINAC and the only system that is capable of automatic targeting corrections based on frequent orthogonal X-ray imaging combined with other tracking techniques used depending on the application [19-21]. Image-guided radiosurgery uses intrafractional image guidance to locate the tumor during a treatment session and redirect the radiation source or reposition the patient based on these measurements. The accuracy of dose delivery using image-guided radiosurgery is comparable to that of frame-based intracranial radiosurgery.

Review

Radiation Therapy for Palliation of Spinal Metastases

External beam radiotherapy

Radiotherapy is a cornerstone of the treatment of spinal metastases, especially in patients with contraindications for surgery, limited disease, and radiosensitive lesions. In general, lymphomas, myeloma, and seminomatous germ-cell tumors are highly radiosensitive. Most solid tumors, such as breast cancer, prostate cancer, and lung cancer, are considered to have intermediate radiosensitivity. Melanomas, osteosarcomas, and renal cell carcinomas are usually considered to be radioresistant [22-24]. Radiotherapeutic options include conventional external beam radiotherapy (EBRT) and more advanced techniques, such as intensity-modulated radiotherapy (IMRT), stereotactic radiosurgery, stereotactic radiotherapy, and systemic application of radio-isotopes.

Multifraction regimens, such as 2400 cGy in six fractions or 3000 cGy in 10 fractions, are commonly used for the treatment of metastases. Nevertheless, the Radiation Therapy Oncology Group Protocol No. 74-02 (RTOG 74-02) trial [25], the study of the Bone Pain Trial Working Party in the United Kingdom [1], and the Dutch Bone Metastasis study [5] in the Netherlands have demonstrated no consequential difference between single-fraction radiotherapy and multifraction schemes. A single dose of 8 Gy has, accordingly, gained widespread acceptance with response rates for pain relief of about 70-80% [5]. The efficacy of this single-fraction scheme was also confirmed by different meta-analytic studies. Sze, et al. [26] published a systematic review comparing short-versus long-course radiotherapy for bone metastases. Three studies reported data on 2,206 randomized patients, 739 of whom had spinal metastases. In this subgroup, the single-fraction treatment was as effective as the multifraction therapy in relieving pain.

Though the immediate control of pain can be achieved with a single dose of 8 Gy, all of the studies mentioned above reported that the incidence of repeat treatment is higher after single-fraction radiotherapy. The question then arises whether higher doses are needed for a longer term control of pain and tumor growth. Higher doses, however, require different techniques of radiation delivery capable of providing higher conformality in order to spare nearby radiosensitive structures, such as the spinal cord.

Radiosurgery

Several studies have demonstrated that radiosurgery is feasible and effective for palliation of spinal metastases. CyberKnife radiosurgery has been used and reported much more than other modalities of spinal radiosurgery, due to the intrinsic ability of the system to provide accurate single stage irradiation to the spine. A limited number of studies reporting the outcome of spinal radiosurgery using the Novalis and the Hi-Art systems will be discussed first. Ryu and co-workers reported results of a clinical feasibility study in 10 patients treated with radiosurgery for spinal metastases with the Novalis system [9]. Radiosurgery (6-8 Gy in a single fraction) was administered as a boost after external beam radiotherapy (25 Gy in 10 fractions). After a median follow-up of six months, all patients had some pain relief, five leading to medication reduction. In another study [27], 31 patients with symptoms of pain and/or neurological deficits were treated with the same technique for 35 tumors, 26 of which were spinal metastases. External beam radiotherapy (25 Gy in 10 fractions) was followed by a single-fraction radiosurgical boost of 6 to 8 Gy. Patients who had previously received 30 Gy with external beam radiotherapy were given a boost of 10 Gy in two fractions. Thirty-two patients experienced pain relief within 72 hours and 22 showed durable neurological improvement. The incidence of complications related to radiosurgery was fairly low, with two patients developing transient radiculitis, and one showing severe neurological deterioration. The Novalis system has also been used for radiosurgery of patients that had not previously received any radiotherapy [28]. In one such study, 49 patients with 61 spinal lesions were treated with single-fraction doses ranging from 10 to 16 Gy, with pain control as the primary endpoint. The authors reported complete pain relief in 37.7%, partial pain relief in 47.6%, and stable symptoms in 16.2% of cases at eight weeks after treatment. De Salles, et al. [19] reported on the treatment of 14 patients with 22 spinal lesions. Following Novalis radiosurgery, 50% of the patients experienced improvement in their pain. Tumor control was achieved in 56% of spinal tumors. The Hi-Art helical tomotherapy system has been used by Kim, et al. [29] for fractionated radiosurgery of spinal metastases. A series of eight patients were treated with doses of 15-30 Gy in one to five fractions. Two patients were treated with a single dose of 15 Gy. All of the treated patients experienced complete radiographic control. Pain control was achieved in all four patients who had follow-up with regard to pain control. An unspecified number of patients with spinal metastases were treated at the University of Virginia's radiosurgery program using a radiosurgical dose of 18–24 Gy to treat spinal metastases. Overall, a fairly rapid pain relief (often within one week) was observed, as assessed by the visual analog pain scale in these patients. A smaller than 8-Gy dose to the region of the spinal cord immediately adjacent to the levels involved in metastatic disease was recommended to avoid spinal cord complications.

At the University of Pittsburgh Medical Center, the largest clinical series to date has been treated with single-fraction CyberKnife radiosurgery [23]. The study involved 500 lesions in 393 patients with metastases of various histologies, mostly renal cell, breast, lung, and melanoma. Goals of the study included tumor control, palliation of symptoms, and restoring neurological function. The average maximum dose to the tumor was 19 Gy in a single fraction. Sixty-seven patients had not been previously irradiated. In 48 of these cases, a significant decrease in pain was observed during the follow-up period of six-48 months (median 16 months). Authors reported long-term radiographic control in 88% of all cases, and 100% for breast, lung, and renal cell carcinoma treated for the first time. Overall long-term pain relief was obtained in 290 of the 336 cases that presented with pain as the primary symptom (86%).

Similar local control results were obtained in a series of 58 patients treated at the Georgetown University Hospital for various metastatic lesions with a dose of 21.16 Gy in 3.6 fractions on average [30]. Most patients were treated for pain rather than other symptoms. Authors reported a rapid and durable pain relief in the short-term. In a very recent article, the same team reported on a prospectively treated 200-patient cohort that consisted of 151 patients with metastases, 36 patients with benign, and 13 patients with malignant spinal tumors. The patients who had not received previous radiation received a mean dose of 26.3 Gy in three fractions and those with pre-CyberKnife radiation history were treated with a mean 21.05 Gy in three fractions. In this study, the pain scores declined from 40.1 to 28.6 post-treatment and continued to decline in the following four years. The authors also noted a significant improvement in the quality of life component.

CyberKnife was also used by Gibbs, et al. [31] for radiosurgery of 74 patients with 102 metastatic lesions. Doses ranged between 16 and 25 Gy in one to five fractions. Two-thirds of the patients had been previously irradiated. Symptoms, including pain and neurological deficits, improved in 84% of cases. Severe myelopathy related to radiosurgery occurred in three patients after a mean of seven months from treatment. The same Stanford team, in collaboration with University of Pittsburgh researchers, recently published a much larger study (1,075 patients) focusing on safety of the CyberKnife radiosurgery of the spine, particularly in terms of delayed myelopathy. Only six patients experienced this adverse event at a median 6.3 months following the treatment. Three of these patients had had previous radiation treatment, three had metastatic, and three benign tumors. Also, half of the afflicted patients had received a BED above 8 Gy to the spinal cord. The authors recommended limiting this dose [32].

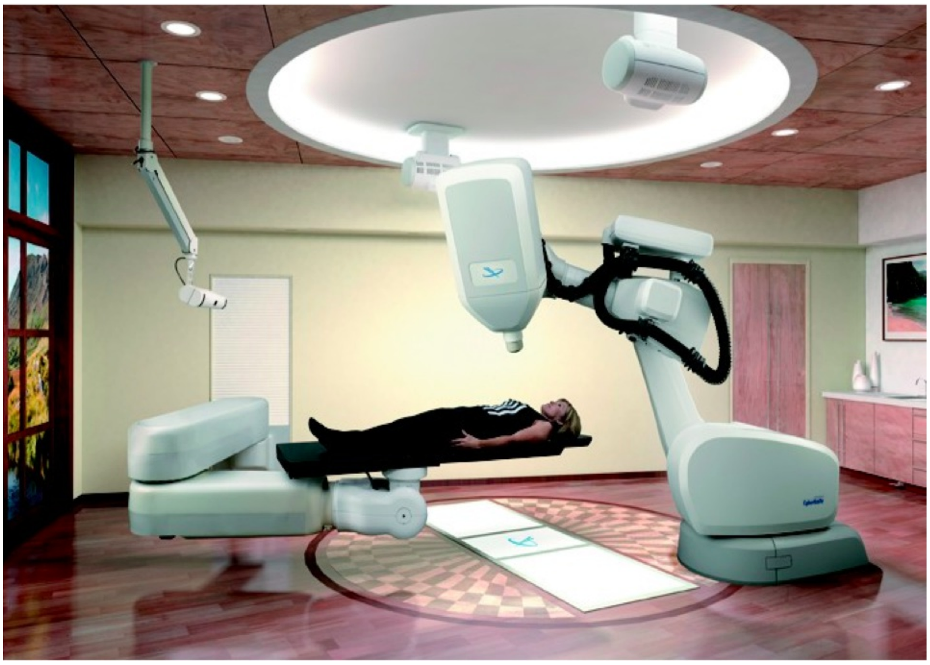

FIGURE 1: CyberKnife robotic, image-guided, stereotactic radiosurgery system.

Future perspectives

Although spinal radiosurgery remains in its infancy, the data reported in the literature clearly show an effective role for it in the treatment of spinal metastases. Stereotactic delivery of radiation to metastatic lesions near the spinal cord can result in good tumor control, rapid and durable pain relief, and in some cases, recovery of neurologic function with little evidence of radiation-related side-effects or radiation necrosis. The largest studies of spinal radiosurgery have consistently shown excellent clinical outcomes without complications using single-fraction approaches. Gerszten, et al. presented outcome of a 115-patient study, including 108 metastatic lesions [33]. They treated all patients with a mean single-fraction dose of 14 Gy (12-20 Gy) prescribed to the 80% isodose line. No acute radiation toxicity or new neurological deficits occurred during the follow-up period (median, 18 months). Axial and radicular pain improved in 74 of 79 patients. In the large-scale study from the same group, not a single instance of radiation-induced neurological complications was observed.

Taken along with the current findings, pain control and local control after single-fraction or hypofractionated radiosurgery are equivalent. This is consistent with results of randomized studies that have failed to show significant difference in pain control between single- and multifraction regimens for external-beam radiation therapy. We can conclude that single-fraction radiosurgery is effective in most cases of spinal lesions, and that hypofractionated radiosurgery should be reserved for treatment of special cases (e.g., larger tumors). The efficacy and safety of highly conformal radiation therapy against metastatic spinal lesions appears to be well-established, based on the data in the literature. However, several questions remain open. Is radiosurgery a viable option as salvage treatment for those who have already undergone conventional radiotherapy, yet demonstrate persistent symptoms and/or radiological progression; or as an initial treatment for patients with limited spinal disease, favorable overall performance status, and focal neurological symptoms? Dose and fractionation schemes are currently chosen on the basis of personal experience and beliefs: a more systematic approach has not been developed yet. Finally, control of tumor progression and palliation of symptoms are two disparate goals of any treatment that must be addressed on a case-by-case basis.

Conclusions

Spinal radiosurgery is a fast, non-invasive treatment used with good results in a growing number of patients with vertebral metastatic pain. In particular, radiosurgery is rapidly becoming the main treatment option for patients with stable vertebral disease, offering high rates of pain and tumor growth control and low incidence of neurological complications.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Yarnold JR: 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. Radiother Oncol . 1999, 52:111-121.
2. Vrionis FD, Miguel R: Managment of spinal metastases . Seminars in Pain Medicine. 2003, 1:25-33.
3. Katagiri H, Takahashi M, Inagaki J, Kobayashi H, Sugiura H, Yamamura S, Iwata H: Clinical results of nonsurgical treatment for spinal metastases. Int J Radiat Oncol Biol Phys . 1998, 42:1127-1132.
4. Ryken TC, Eichholz KM, Gerszten PC, Welch WC, Gokaslan ZL, Resnick DK: Evidence-based review of the surgical management of vertebral column metastatic disease. Neurosurg Focus. 2003, 15:E11.
5. Steenland E, Leer JW, van Houwelingen H, Post WJ, van den Hout WB, Kievit J, de Haes H, Martijn H, Oei B, Vonk E, van der Steen-Banasik E, Wiggenraad RG, Hoogenhout J, Warlam-Rodenhuis C, van Tienhoven G, Wanders R, Pomp J, van Reijn M, van Mierlo I, Rutten E: The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. Radiother Oncol . 1999, 52:101-109.
6. Maranzano E, Latini P, Perrucci E, Beneventi S, Lupattelli M, Corgna E: Short-course radiotherapy (8 Gy x 2) in metastatic spinal cord compression: an effective and feasible treatment. Int J Radiat Oncol Biol Phys. 1997, 38:1037-1044.
7. Rades D, Schild SE: Is stereotactic radiosurgery the best treatment option for patients with spinal metastases?. Nat Clin Pract Oncol. 2007, 4:400-401.
8. McLoughlin GS, Sciubba DM, Wolinsky JP: Chondroma/Chondrosarcoma of the spine . Neurosurg Clin N Am . 2008, 19:57-63.
9. Ryu S, Fang Yin F, Rock J, Zhu J, Chu A, Kagan E, Rogers L, Ajlouni M, Rosenblum M, Kim JH: Image-guided and intensity-modulated radiosurgery for patients with spinal metastasis. Cancer. 2003, 97:2013-2018.
10. Dodd RL, Ryu MR, Kamnerdsupaphon P, Gibbs IC, Chang SD, Jr., Adler JR, Jr.: CyberKnife radiosurgery for benign intradural extramedullary spinal tumors. Neurosurgery. 2006, 58:674-685.
11. Chopra R, Morris CG, Friedman WA, Mendenhall WM: : Radiotherapy and radiosurgery for benign neurofibromas. Am J Clin Oncol. 2005, 28:317-320.
12. Chuang CC, Chang CN, Tsang NM, Wei KC, Tseng CK, Chang JT, Pai PC: Linear accelerator-based radiosurgery in the management of skull base meningiomas. J Neurooncol . 2004, 66:241-249.
13. Barnett GH, Linskey ME, Adler JR, Cozzens JW, Friedman WA, Heilbrun MP, Lunsford LD, Schulder M, Sloan AE: Stereotactic radiosurgery--an organized neurosurgery-sanctioned definition . J Neurosurg. 2007, 106:1-5.
14. Leksell L: The stereotaxic method and radiosurgery of the brain . Acta Chir Scand . 1951, 102:316-319.
15. Hamilton AJ, Lulu BA, Fosmire H, Stea B, Cassady JR: Preliminary clinical experience with linear accelerator-based spinal stereotactic radiosurgery. Neurosurgery. 1995, 36:311-319.
16. Adler JR, Jr., Chang SD, Murphy MJ, Doty J, Geis P, Hancock SL: The Cyberknife: a frameless robotic system for radiosurgery. Stereotact Funct Neurosurg. 1997, 69:124-128.
17. Romanelli P, Adler JR, Jr.: Technology Insight: image-guided robotic radiosurgery--a new approach for noninvasive ablation of spinal lesions. Nat Clin Pract Oncol . 2008, 5:405-414.
18. Avanzo M, Romanelli P: Spinal radiosurgery: technology and clinical outcomes . Neurosurg Rev. 2009, 32:1-12; discussion 12-13.
19. De Salles AA, Pedroso AG, Medin P, Agazaryan N, Solberg T, Cabatan-Awang C, Espinosa DM, Ford J, Selch MT: Spinal lesions treated with Novalis shaped beam intensity-modulated radiosurgery and stereotactic radiotherapy. J Neurosurg. 2004, 101:435-440.
20. Muacevic A, Staehler M, Drexler C, Wowra B, Reiser M, Tonn JC: Technical description, phantom accuracy, and clinical feasibility for fiducial-free frameless real-time image-guided spinal radiosurgery. J Neurosurg Spine . 2006, 5:303-312.
21. Sahgal A, Larson DA, Chang EL: Stereotactic body radiosurgery for spinal metastases: a critical review . Int J Radiat Oncol Biol Phys . 2008, 71:652-665.
22. Gerszten PC, Burton SA, Ozhasoglu C, Vogel WJ, Welch WC, Baar J, Friedland DM: Stereotactic radiosurgery for spinal metastases from renal cell carcinoma. J Neurosurg Spine . 2005, 3:288-295.
23. Gerszten PC, Burton SA, Ozhasoglu C, Welch WC: Clinical experience in 500 cases from a single institution . Spine. 2007, 32:193-199.
24. Gerszten PC, Burton SA, Quinn AE, Agarwala SS, Kirkwood JM: Radiosurgery for the treatment of spinal melanoma metastases. Stereotact Funct Neurosurg . 2005, 83:213-221.
25. Tong D, Gillick L, Hendrickson FR: The palliation of symptomatic osseous metastases: final results of the Study by the Radiation Therapy Oncology Group. Cancer. 1982, 50:893-899.
26. Sze WM, Shelley M, Held I, Mason M: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials. Cochrane Database Syst Rev. 2004, 2:CD004721.
27. Benzil DL, Saboori M, Mogilner AY, Rocchio R, Moorthy CR: Safety and efficacy of stereotactic radiosurgery for tumors of the spine. J Neurosurg. 2004, 101:413-418.
28. Ryu S, Jin R, Jin JY, Chen Q, Rock J, Anderson J, Movsas B: Pain control by image-guided radiosurgery for solitary spinal metastasis. J Pain Symptom Manage. 2008, 35:292-298.

29. Kim B, Soisson ET, Duma C, Chen P, Hafer R, Cox C, Cubellis J, Minion A, Plunkett M, Mackintosh R: Image-guided helical Tomotherapy for treatment of spine tumors. Clin Neurol Neurosurg. 2008, 110:357-362.
30. Degen JW, Gagnon GJ, Voyadzis JM, McRae DA, Lunsden M, Dieterich S, Molzahn I, Henderson FC: CyberKnife stereotactic radiosurgical treatment of spinal tumors for pain control and quality of life . J Neurosurg Spine . 2005, 2:540-549.
31. Gibbs IC, Kamnerdsupaphon P, Ryu MR, Dodd R, Kiernan M, Chang SD, Adler JR, Jr.: Image-guided robotic radiosurgery for spinal metastases. Radiother Oncol. 2007, 82:185-190.
32. Gibbs IC, Patil C, Gerszten PC, Adler JR, Jr., Burton SA: Delayed radiation-induced myelopathy after spinal radiosurgery. Neurosurgery. 2009, 64:A67-72.
33. Gerszten PC, Ozhasoglu C, Burton SA, Vogel WJ, Atkins BA, Kalnicki S, Welch WC: CyberKnife frameless single-fraction stereotactic radiosurgery for benign tumors of the spine. Neurosurg Focus . 2003, 14:e16.