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Novalis radiosurgery for metastatic spine tumors

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For many cancers, the spine is the most frequent site of metastatic disease. Many patients develop neurologic manifestations of spinal cord or cauda equina compression, presenting with complaints that include back pain, weakness, sensory deficits, and bowel and bladder changes [1]. Left untreated, a large percentage of these patients become paraplegic. It is well known that effective treatment at a time when the patient is still ambulatory leads to the best chance for maintenance of excellent quality of life [2].

The goals of therapy for patients with spinal metastases include pain control; the prevention, stabilization, or restoration of neurologic deficits; and local control of neoplastic progression. Although bony instability secondary to metastatic disease and its potential for neurologic compromise is a significant concern with these patients, this article does not address this issue. To date, standard treatment for metastatic spine tumors has included pain medications and steroids, surgical decompression, radiation therapy, and, in certain circumstances, chemotherapy, with the mainstay of therapy for neoplastic spinal cord compression associated with neurologic deficit being surgical decompression followed by radiation therapy. The surgery-based strategy is used primarily for patients with spinal instability or compression fracture with retropulsion into the spinal canal or the acute onset and progression of neurologic symptoms secondary to spinal cord compression. The effectiveness of these paradigms is well established when administered while patients remain ambulatory. In the general population of patients with neoplastic spine disease with or without symptomatic spinal cord compression, however, external beam radiation therapy (EBRT) using generous margins (one or two vertebral segments) has been the primary treatment and also has been well established. In this population, varying degrees of pain relief and neurologic improvement have been reported [3,4].

Radiosurgery delivers a highly conformal and large radiation dose to a localized tumor by a stereotactic approach. This process requires precise target definition and immobilization or, most recently, accurate tracking of the target organ during irradiation. Metastatic lesions involving the vertebra are usually irregular in shape and often are associated with a paravertebral mass. The combination of the need to conform the dose accurately to an irregular target and to limit the dose of radiation delivered to nearby organs at risk (ie, spinal cord) makes the use of radiosurgery more challenging. To avoid radiation-induced injury of the spinal cord, the irregular lesion can be targeted by way of multiple beam orientations, each shaped by micro-multileaf collimation. In addition, intensity modulation of each radiation beam (ie, varying the delivered dose per beam) helps to increase the conformality and homogeneity of radiation to the tumor while minimizing the radiation dose to the spinal cord. Image-guided shaped-beam radiosurgery is capable of not only shaping the radiation beam by using micro-multileaf collimation but of localizing the lesion using a new noninvasive infrared marker technology for positioning. Formerly, the main obstacle to the application of extracranial radiosurgery was organ motion associated with general patient movement or respiration and

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a lack of convenient immobilization techniques. Among the extracranial target organs, the spinal cord and vertebrae are associated with the least breathing-related organ movement, making the spinal cord and vertebrae particularly suitable for stereotactic radiosurgery. Initial experience with spinal radiosurgery required a cumbersome and invasive procedure that anchored the stereotactic frame to the spinous process under general anesthesia [5]. Preclinical and clinical studies were performed at our institution to determine the accuracy and precision of the shaped-beam radiosurgery unit and the potential role of spinal radiosurgery for the treatment of spinal metastasis and cord compression [6].

Materials and methods

The image-guided shaped-beam radiosurgery program at Henry Ford Hospital (HFH) uses the Novalis system (BrainLAB, Ammerthalstrabe, Germany). It was installed at HFH in April 2001. Since the inception of the extracranial radiosurgery program, 140 treatments in 110 patients with primary and metastatic spine and spinal cord tumors have been performed as of August 2003. Most of these patients were previously untreated patients with spinal metastases and previously treated patients with recurrent spinal metastases.

Basic system

The Novalis Shaped-Beam Surgery unit (BrainLAB) is equipped with a built-in micromultileaf collimator (mMLC) and a single 6-MV photon energy linear accelerator. There are 26 pairs of leaves (14 pairs with a leaf width of 3 mm, 6 pairs with a leaf width of 4.5 mm, and 6 pairs with a leaf width of 5.5 mm), which form a maximum field size of 10 cm $\times$ 10 cm [7]. Radiation can be delivered through circular cone arcs, fixed-shape conformal beams using mMLC, fixed-shape conformal arcs using mMLC, dynamic-shape conformal arcs using mMLC, and a fixed gantry with static and dynamic intensity modulation beams.

Delivery precision is accomplished with a patient immobilization method, an automated patient positioning device, and various image-guided target localization devices (ExacTrac and Novalis Body system, BrainLAB). The ExacTrac device is made up of a computerized control system and two infrared cameras that detect infrared-sensitive markers placed on the patient's skin and compare marker location with stored information, which then prompts the treatment machine to move the patient (ie, target isocenter) to the preplanned location on the treatment couch. The Novalis Body system is a video camera system that verifies patient location and is composed of two keV x-ray tubes, an amorphous silicon flat-panel digital detector, and a computerized control and image analysis system. The Novalis Body system generates two digitally reconstructed radiographs from the simulation computed tomography (CT) scan at the same orientation as the two keV x-ray images. The system then automatically compares internal structures (eg, vertebral body images) noted in the keV images with those in the digitally reconstructed images and indicates potential isocenter deviations, which the radiation oncologist notes and forwards to the ExacTrac device, which then adjusts patient position. This automated process is based on the integration of the ExacTrac and Novalis Body system with the treatment machine.

Patient simulation

The patient is simulated in the supine position using a large-bore AcQStim CT simulator (Phillips Medical Systems, Cleveland, OH). The combination of a vacuum body-fixing device (BodyFix; Medical Intelligence, Feyerabendstrabe, Germany) and an alpha cradle provides maximum patient stability. Infrared-sensitive markers are placed on the patient's skin in such a way as to be seen on the CT (slice thickness of 3 mm) images. The digital image communication practice CT images are then sent to the treatment planning system.

Treatment planning

The clinical target volume (CTV) and critical organs are identified for planning. Generally, targets have not consisted of more than one or two vertebral body segments. The planning target volume consists of an additional 2 to 3 mm to that of the CTV to accommodate positioning variations.

Most treatment plans for spinal radiosurgery involve multiple intensity-modulated beams (ranging from five to nine) to minimize the dose to critical organs. Dynamic-shaped conformal arcs have also been used for tumors in locations distant to the spinal cord and cauda equina (eg, sacrum). In our early experience, the typical plan

for spinal radiosurgery has included seven coplanar intensity-modulated beams generated using an inverse treatment planning algorithm developed based on the dynamically penalized likelihood method and a pencil beam dose calculation algorithm [8]. Dose-volume histograms were used to identify appropriate doses for target and critical organs and to evaluate treatment plans. In each instance, four inverse plans were generated for comparison; in addition, the conformity index was used to evaluate the treatment plan. After identification of a suitable inverse plan, the treatment data were exported to the Varis record-and-verify system using radiation treatment planning exchange software (Varian Software Systems, Palo Alto, CA). At the same time, the patient positioning information was exported to the ExacTrac and Novalis Body system.

Quality assurance

As part of the quality assurance procedure, the final treatment plan is checked in terms of monitor unit (MU) calculations, intensity maps, and isocenter doses in the verification phantom. The treatment machine and image-guided patient positioning devices are calibrated daily. An independent algorithm based on a modified Clarkson method was developed to calculate the isocenter dose contributed by each mMLC segment and its corresponding MUs for all segments of each intensity-modulated beam. The intensity map was verified by giving a fraction of the dose of each intensity-modulated beam (Fig. 1). Resulting film-based intensity maps were compared with planned intensity maps; the absolute point dose was verified by exporting planned intensity maps to the verification phantom, and the isocenter dose in the phantom was calculated. The phantom was then irradiated with all intensity-modulated beams, and the isocenter dose of the phantom was measured in a micro-ion chamber (Exradin T14; Standard Imaging, Middletown, WI) with a sensitive volume of 0.009 mL and compared with planned isocenter doses.

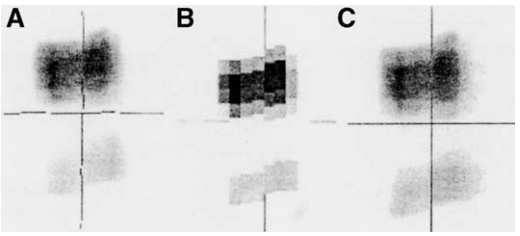

Fig. 1. Intensity map film image delivered with the dynamic micro-multileaf collimator technique (*A*) and the corresponding intensity map from the treatment plan (*B*). (*C*) The intensity map film image delivered with the step-and-shoot technique. (*From* Yin F-F, Ryu S, Ajlouni M, et al. A technique of intensity-modulated radiosurgery (IMRS) for spinal tumors. Med Phys 2002;29:2815–22; with permission.)

Treatment

Repositioning of the patient was performed with the assistance of the ExacTrac and Novalis Body system. For the verification of patient position, internal structures are compared by fusion of the two images taken by Novalis Body system and the simulator. The information on isocenter deviation is automatically forwarded to the ExacTrac device for adjustment of position. The ExacTrac moves the patient into the final position. Orthogonal portal films were then taken for final verification by the radiation oncologist immediately before treatment. This final portal film may not be absolutely necessary but was included in our early experience to provide the treating physicians with a margin of comfort. These orthogonal portal films were also used to determine the accuracy of the isocenter in the treatment position under our first protocol of the clinical feasibility study of spinal radiosurgery.

Results

Preclinical studies for extracranial radiosurgery included dosimetric and technical descriptions and validation of the techniques in the phantom [6]. The initial technical validation was described from the experience of the first 25 patients with various spinal tumors, mostly recurrent tumors in the spine [6]. The first protocol of the clinical feasibility study was developed as a phase I study to determine the accuracy and precision of spinal radiosurgery for the treatment of single spinal metastasis [9]. Encouraged by the results for precision from the clinical feasibility study, we continued dose escalation of spinal radiosurgery for previously untreated single spine metastasis from 10 to 16 Gy in 2-Gy increments (unpublished results).

The initial experience for technical validation included 25 patients with mostly recurrent spinal tumors, with the dose ranging from 6 to 12 Gy [6]. Most patients were simulated within 48 hours of treatment. In general, the overall process,

including simulation, planning, and treatment, required between 3 and 4 hours, with a beam delivery time of approximately 20 to 30 minutes. On average, seven dynamic intensity-modulated beams (90%) or dynamic conformal arcs (7%) were used in a predominantly coplanar arrangement. The dose to the clinical target was prescribed to the 90% isodose line. Final phantom verification of isocenter doses indicated that the average deviation of measured isocenter doses from planned isocenter doses for all patients treated with intensity-modulated beams was less than 2%. Film dose measurement in a phantom study indicated excellent agreement between measured and planned isodose lines greater than 50%.

The first primary spinal tumor treated with radiosurgery was recurrent Ewing's sarcoma in the lumbar spine [10]. This patient had first been operated on in 1995 and treated with radiation therapy (total dose of 6500 cGy) after diagnosis. Recurrent symptoms 2 years later prompted a second operation, followed by multiagent chemotherapy; however, despite these efforts, recurrent tumor associated with severe pain only partially responsive to narcotics in the lower extremities was identified in 2002. After discussion at the neuro-oncology tumor board, no additional chemotherapy was considered useful and spinal radiosurgery was administered. Two weeks after treatment (12 Gy delivered with seven coplanar beams), the patient experienced significant and dramatic pain relief. On magnetic resonance imaging (MRI) imaging 6 weeks after treatment, it was noted that the tumor had been significantly debulked (Fig. 2). At the last follow-up 18 months after treatment, the patient continues to experience pain relief and there is no indication of progression on MRI.

A clinical feasibility study was designed to determine the accuracy and precision of radiosurgery in 10 patients with pathologically proven spinal metastasis that had not been treated previously [9]. Patients with tumors involving one or two contiguous vertebral segments with and without spinal cord compression were included in this study. To achieve the therapeutic effect of pain control, the patients were treated with EBRT (25 Gy in 10 fractions), followed by boost radiosurgery (6–8 Gy). The accuracy of the final isocenter was verified with image fusion by two radiation oncologists by comparing a single portal film taken in the treatment room immediately before treatment with the system-generated radiographs. In this fashion, the precision or degree of variation between the isocenters of the CT-generated simulation images and the final portal films (ie, actual final patient position taken at the time of delivery) was within 1.36 ± 0.11 mm. Importantly,

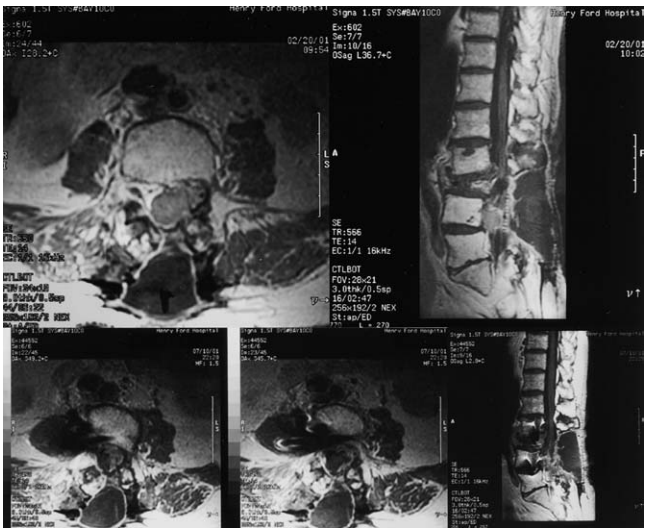

Fig. 2. (*Top*) Axial and sagittal projections of T1-weighted gadolinium-enhanced MRI images from February 2001. (*Bottom*) Axial and sagittal projections of T1-weighted gadolinium-enhanced MRI images from July 2001. (*From* Rock J, Kole M, Yin FF, Ryu S, Gutierez J, Rosenblum M. Radiosurgical treatment for Ewing's sarcoma of the lumbar spine. Spine 2002;27(21):E472–5; with permission.)

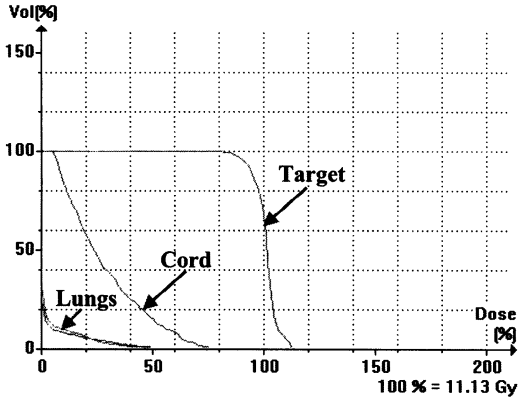

Fig. 3. Dose-volume histogram for most cases of intensity-modulated spinal radiosurgery. (*From* Yin F-F, Ryu S, Ajlouni M, et al. A technique of intensity-modulated radiosurgery (IMRS) for spinal tumors. Med Phys 2002;29:2815–22; with permission.)

the spinal cord dose-volume effect was minimized with generally less than 10% of the anterior spinal cord volume included in 80% of the prescribed dose (Fig. 3). Although it was not the primary goal of this study, clinical outcomes of pain control and neurologic improvement were assessed. Eight of eight patients experienced significant pain relief, with five requiring reduced medication. Average time to pain relief ranged between 2 and 4 weeks. Two patients presented with incomplete paraplegia (0/5 muscle power) before treatment; one patient with Hodgkin's disease experienced complete recovery to normal lower extremity power (5/5) and complete resolution of tumor on MRI. The other patient with prostate cancer noted only partial recovery (3/5). In a mean follow-up of 6 months (range: 3–12 months), no radiation toxicity was noted clinically [9].

Subsequent radiosurgery dose escalation was performed in patients with a single or two contiguous spine metastases with radiosurgery doses of 10 to 16 Gy in a single dose with a 2-Gy increment without EBRT (unpublished results). In each dose cohort, 10 to 15 patients were allocated. The goal of this study was to determine the optimum radiosurgery dose and to validate radiosurgery of the involved spine as the primary treatment. Every effort was made to detect clinical, neurologic, and radiologic tumor control as well as adverse effects to the spinal cord in particular. This study was analyzed with a median follow-up of 13 months (range: 3–24 months). Pain control was assessed by means of a visual analog scale. Pain control was defined as complete relief, and pain reduction was defined as a decrease of at least three points. Rapid pain control was achieved with a median time to pain control/reduction of 14 days after radiosurgery. The earliest pain control was seen as early as 24 hours. Durable pain relief was achieved with a median duration of pain relief/reduction of 13 months. Pain control was more significant in the higher dose group above 14 Gy. Radiologic tumor control was also seen in patients with an epidural mass or soft tissue tumor component. One example of complete tumor control is shown in Fig. 4. Neurologic improvement was seen in 6 of 8 patients. Three of 5 patients with spinal cord compression were treated with radiosurgery alone and had complete neurologic recovery. There was no detectable acute or subacute radiation toxicity noted clinically during the maximum follow-up interval of 24 months.

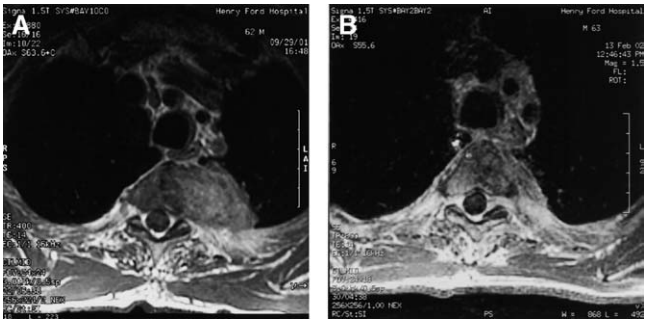

Fig. 4. (*A*) Non-small cell lung cancer before radiosurgery. (*B*) The same lesion 6 months after radiosurgery.

Discussion

All radiosurgical applications require accurate delivery of radiation based on precise target localization and immobilization. Whereas target localization for cranial radiosurgery has traditionally been achieved with head frames, and recently with form-fitted masks, target localization for extracranial radiosurgery has only recently been ensured. Advances in digital imaging and high-speed computer computations have been critical to the development of this technology. The image-guided frameless radiosurgical systems can now deliver large highly conformal doses of radiation to various organs and the spine with limited inconvenience to the patient and the assurance of accurate delivery.

The radiosurgical system must be able to generate a highly conformal dose distribution with millimetric precision to the lesion while sparing at-risk critical structures, including the spinal cord. The system must be able to recognize and correct for patient movement throughout the treatment period. Stereotaxy for spinal radiosurgery can be achieved by a frame-based or frameless method. Frame-based stereotactic devices have included fixed cranial frames or head and neck masks that act as fiducial boxes and fixed stereotactic body frames [5]. Frameless stereotactic methods use guided imaging directed by either metallic markers implanted around a tumor region or surrogate digital anatomy, such as adjacent bony structures. All systems must comply with recommendations of the treatment unit manufacturer and specified clinical tolerances. The accuracy of the Novalis system is based on computer algorithms that identify vertebral anatomy (ie, directly defining the radiosurgical target) from the digitally reconstructed simulation CT and by virtue of an integrated movement tracking system that moves the supine positioned patient into phase with keV images taken immediately before treatment, superimposing vertebral anatomy, thereby placing the target at the radiosurgical isocenter. Our clinical feasibility study demonstrated that the average isocenter deviation between the planned target isocenter and the actual treatment isocenter within the patient at the treatment position is 1.36 ± 0.11 mm [6,9]. This degree of precision is clinically acceptable for radiosurgical procedures. We are currently in the process of developing a three-dimensional treatment verification system using an image reconstruction method. Other spinal radiosurgical systems use surgically implanted fiducials fixed to the vertebrae to accommodate the clinical problem of patient movement [11]. During the treatment process, the Novalis radiosurgery unit is capable of updating patient position and readjusting the treatment couch to bring the target volume back to the treatment isocenter. Accurate patient positioning and repositioning are achieved by means of an automated positioning process. Maintaining patient comfort throughout the duration of treatment (approximately 30 minutes) is critical and achievable.

A clinical issue critical for spinal radiosurgical treatment relates to the radiation tolerance of the spinal cord and cauda equina. Factors that may affect the spinal cord tolerance include but are not limited to the timing and pattern of radiation dose fractionation, volume and length of the cord, age, patient condition, and other associated oncologic treatments with chemotherapy and surgery [12]. There is no literature that directly relates the biologic effects for single radiosurgical doses to the spinal cord. From our first application at HFH, a spinal cord tolerance dose of 800 cGy has been elected; this is based primarily on previously reported optic apparatus tolerance [13]. In subsequent dose escalation analysis, up to 16 Gy to the spinal target has been used, and we have not noted any clinically detectable acute or subacute neurologic morbidity with a maximum follow-up of 24 months (unpublished results). In addition, follow-up MRI scans have not demonstrated any detectable signal changes within the spinal cord, although longer follow-up might be needed. Based on these data, we now believe that the tolerance of partial volume spinal cord might be at least 10 Gy to not more than 10% of spinal cord volume. In our series, the main factors affecting the radiation dose distribution to the spinal cord were the prescribed radiosurgery dose and number of beams used. In these patients, the use of intensity modulation has allowed all target volumes to be irradiated without a significant adverse effect on the spinal cord. Further studies are in progress to determine the tolerance dose to the partial spinal cord and the nature of other contributing factors.

Overall, our experience has demonstrated a significant potential for spinal radiosurgery in the treatment of spinal metastasis with or without cord compression. A significant degree of pain relief was achieved in a relatively short time (within 2 weeks) in most patients, and pain relief seems to be more reliably achieved with higher radiosurgery doses (ie, >14 Gy) to the tumor

periphery. This rapid pain relief will further improve the quality of life of the patients. Additional factors of convenience for patients include the reduction to a single or several hospital visits for complete treatment.

Radiosurgery has become a viable treatment option for brain metastasis, either alone or combined with EBRT. Given that definitive treatment with radiosurgery alone for single or multiple brain metastases has resulted in excellent local control of tumor and, in some cases, improved neurologic function, it is reasonable to expect that a similar approach for spinal metastasis will be found. Based on our experience, we are currently running an institutional review board–approved protocol that is designed to establish a database and define various outcomes for patients managed with spinal radiosurgery. All patients (eg, previously untreated and treated) will be included. The primary outcomes analyses include clinical (ie, pain control instruments, neurologic examination), oncologic (ie, MRI follow-up), and quality of life (ie, patient self-report, other validated instruments) components. This multidisciplinary approach protocol involves the Departments of Radiation Oncology, Clinical Oncology, Neurosurgery, and Diagnostic Radiology.

Summary

It is logical to anticipate that the field of spinal radiosurgery will evolve in a fashion similar to that seen for intracranial radiosurgery. Given the frequency of various pathologic entities that affect the spine, including those that have proven to be largely intractable to surgery, radiation, and chemotherapy (eg, sarcomas), and the serious clinical, economic and quality-of-life consequences of paraplegia, radiosurgery offers new hope as an adjuvant or primary therapy. The meticulous application of well-designed investigations of relevant clinical outcomes will be critical to the appropriate and effective use of this technology.

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