Stereotactic radiosurgery for spinal metastases from renal cell carcinoma

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Object. The role of stereotactic radiosurgery in treating renal cell carcinoma (RCC) metastases to the spine has previously been limited. In this study the authors evaluated the clinical outcome in patients with spinal RCC who underwent single-fraction radiosurgery.

Methods. Forty-eight patients with 60 RCC metastases to the spine (six cervical, 26 thoracic, 18 lumbar, and 10 sacral) were treated with a single-fraction radiosurgery technique and were followed for a period of 14 to 48 months (median 37 months).

All patients were successfully treated in an outpatient setting. The tumor volume ranged from 5.5 to 203 cm³ (mean 61.9 cm³). Forty-two of the total 60 lesions had been previously treated with external-beam radiation therapy (EBRT). The maximum tumor dose was maintained at 17.5 to 25 Gy (mean 20 Gy). The volume of the spinal cord exposed to greater than 8 Gy ranged from 0.01 to 3 cm³ (mean 0.64 cm³); the volume of the spinal canal at the cauda equina level exposed to greater than 8 Gy ranged from 0.01 to 2.2 cm³ (mean 0.65 cm³). No radiation-induced toxicity occurred during the follow-up period. Axial and radicular pain improved in 34 (89%) of 38 patients who were treated primarily for pain. Tumor control was demonstrated in seven of eight patients treated primarily for radiographically documented tumor progression. In time six patients required open surgical intervention for tumor progression that had caused neurological dysfunction after radiosurgery.

Conclusions. Spinal radiosurgery can be a successful therapeutic modality for the delivery of large-dose single-fraction radiation to RCC spinal metastases that are often poorly controlled with conventional EBRT modalities.

KEY WORDS • renal cell carcinoma • spinal metastasis • CyberKnife • image-guided surgery • robotic surgery • stereotactic radiosurgery

Abbreviations used in this paper: CT = computerized tomography; EBRT = external-beam radiation therapy; IMRT = intensity-modulated RT; LINAC = linear accelerator; MR = magnetic resonance; RCC = renal cell carcinoma; SRS = stereotactic radiosurgery; VB = vertebral body.
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Clinical Material and Methods

This study involved the prospective evaluation of 60 lesions in 48 consecutive patients with RCC metastatic to the spine who underwent CyberKnife radiosurgery in which the Dynamic Tracking System (version 3.0: Accuracy, Inc.) was used. All patients were treated at the University of Pittsburgh Medical Center and the protocol was approved by the university’s institutional review board. The study was designed to test the hypothesis that spinal radiosurgery is safe, feasible, and clinically effective for the treatment of spinal metastatic RCC.

There were 28 men and 20 women who ranged in age from 45 to 84 years (mean 62 years). Table 1 provides a summary of the characteristics of the treatment group, and Table 2 provides a summary of the primary indications for spinal SRS that were used for patient selection in this study. Exclusion criteria for CyberKnife radiosurgery were: 1) evidence of overt spinal instability; and 2) neurological deficit resulting from osseous compression of neural structures.

The CyberKnife System

The CyberKnife consists of a 6-MV compact LINAC that is smaller and lighter in weight than LINACs used in conventional radiotherapy. Its smaller size allows the device to be mounted on a computer-controlled six-axis robotic manipulator that permits a much wider range of beam orientations than can be achieved with conventional radiotherapy devices. Two diagnostic radiographic cameras are positioned orthogonally (90˚ offset) to acquire real-time images of the patient’s internal anatomy during treatment. The images are processed to identify radiographic features (skull bone landmarks or implanted fiducials) and then automatically compared with the CT treatment planning study. The precise tumor position is communicated through a real-time control loop to a computer to ensure that the machine is clinically relevant accuracy of 1.1 mm when using a 1.25-mm CT scan slice thickness.

Overview of Treatment

CyberKnife spinal radiosurgery consists of three distinct components: 1) CT scan acquisition based on skull bone landmarks or implanted fiducials; 2) treatment planning; and 3) the treatment itself. All cervical lesions to the C-7 level were tracked relative to skull bone landmarks. All patients with cervical lesions were fitted with a noninvasive molded Aquaplast facemask (WRF/Aquaplast Corp., Wyckoff, NJ) that stabilized the head and neck on a radiographically transparent headrest. In all other cases the lesion to be treated; this was undertaken using a standard Jamshidi bone marrow biopsy needle (Alliance Healthcare Corp., McGraw Park, IL) as previously described. The fiducial placement procedure was performed in the operating room in an outpatient setting prior to undertaking the CT planning, which was performed using the aforementioned slice thickness. The patient was placed in a conformal alpha cradle during CT scanning and during treatment. We obtained 1.25-mm-thick CT slices that included the lesion of interest and all fiducials.

The second component of the CyberKnife treatment is the development of the radiosurgical treatment plan. Each treatment plan was devised jointly by a team of neurosurgeons, radiation oncologists, and radiation physicists. In each case, the radiosurgical treatment plan was designed based on tumor geometry, its proximity to spinal cord, and its location. Treatment planning was performed using the Accuray treatment planning system (Dynamic Tracking System running version 3.0 software). The tumor dose was determined based on spinal cord tolerance and quantity of previously administered radiation. Dose prescription was based on currently accepted single-fracton doses used for intracranial sites. We also considered cases involving prior radiation exposure and those with lesions close to the spinal cord. The prescription dose was independent of the tumor volume.

In each case, the spinal cord and/or cauda equina was outlined as a critical structure. At the level of the cauda equina, the spinal canal was outlined. Therefore, at the level of the cauda equina, the critical volume is the entire spin-
The mean maximum dose delivered to lumbar and sacral tumors (28 cases) at the level of the cauda equina was 19 Gy and the mean volume in these 28 cases was 85.8 cm³, twice that of the tumors at the level of the spinal cord. The intraoperative dose received by the cauda equina ranged from 0.51 Gy to 14.31 Gy (mean 9.15 Gy). The volume of the cauda equina receiving greater than 8 Gy for these same patients ranged from 0.01 to 2.2 cm³ (mean 0.65 cm³).

Given the kidneys’ relative radiosensitivity, a limit of 2 Gy was set as the maximum dose received by each. Furthermore, in many patients only a single kidney remained. Thirty-one patients had previously undergone a nephrectomy.

Within the cohort, no patient experienced an exacerbation of symptoms, hemorrhage, or new neurological deficit in the immediate posttreatment period. There were no cases of radiation-induced myelopathy or radiculopathy during the follow-up period. The primary indications for CyberKnife treatment and overall clinical outcomes are listed in Table 2. The primary indication for radiosurgery in 38 patients was significant pain secondary to the lesion. Thirty-seven (95%) of 38 patients reported an improvement in pain measured using a 10-point pain scale at the 1-month follow-up examination. Long-term pain improvement was demonstrated in 34 cases (89%). In 28 of the 38 cases treated primarily for pain, the symptomatic lesion had received prior irradiation. There was no association between prior irradiation and symptomatic improvement after radiosurgery. Analogic medication usage was also documented. Three patients underwent a repeated CyberKnife treatment for recurrence of same-level pain at 6, 7, and 18 months after their initial SRS. The maximum treatment doses in these three cases were 17.5 Gy for two and 20 Gy for the third.

Eight patients were treated primarily for an increase in tumor size demonstrated on follow-up imaging; there was no associated neurological deficit or significant pain. All eight patients (eight lesions) had previously undergone EBRT. During a follow-up period ranging from 20 to 29 months, the lesions in seven of these patients were stable at the location of treatment, with none progressing in size within the treatment volume on MR imaging. In the remaining patient, an elective T-10 corpectomy was performed 11 months after SRS to treat progressive kyphosis.

In six cases, spinal SRS was performed as the primary treatment modality for the lesion. These lesions were usually asymptomatic and were observed on imaging studies acquired in patients who were undergoing open decom-

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**TABLE 2**

*Primary clinical indications for SRS in 48 patients with RCC metastases*

<table>
<thead>
<tr>
<th>Indication</th>
<th>Overall No. of Cases</th>
<th>W/ Favorable Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>pain</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>imaging-based tumor progression</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>primary treatment modality</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>postop radiation boost</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>progressive neurological deficit</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

* Tabular values reflect the overall number of lesions (60), not patients.
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Despite advances during the past decade in the surgical treatment of patients with localized RCC, 50% of these lesions and would be used as landmarks when the patients recovered from their surgical procedure, to avoid a protracted course of EBRT. There were no cases of wound healing problems associated with radiosurgery in these open surgery–treated cases. In one case, fiducials were implanted at the time of percutaneous biopsy sampling in a patient with previously unknown metastatic disease. The lesion had been discovered on routine imaging for another indication.

Spinal SRS was undertaken in five patients who had previously undergone an open decompressive surgery. All five had previously undergone EBRT of the lesion prior to progression of the neoplasm that caused neurological deficit and subsequent need for surgery. In three cases, follow-up imaging had revealed tumor progression at the resection site of the lesion. In all five cases, surgical reexploration was thought to be contraindicated, and spinal radiosurgery was elected. Reexploration was believed to be contraindicated because of the poor performance status documented in two patients, previously placed posterior spinal instrumentation that would have complicated a second surgery because of the anterior compression of the thecal sac in two patients, and medical comorbidities that precluded a transthoracic corpectomy in one patient.

In four patients primarily treated with radiosurgery for pain neurological deficits subsequently developed after the treated tumor progressed during the follow-up period (range 14–48 months, median 37 months). All four patients underwent open decompressive surgery. Progression to complete paraplegia occurred during the follow-up period in two patients with lesions treated with radiosurgery.

Two patients underwent SRS for progressive neurological deficit as their primary indication. In both patients spinal cord compression was caused by myelopathy. Myelopathy initially resolved in each but later progressed, and the patients required open decompressive surgery and instrumentation-augmented fixation within 6 months of the CyberKnife treatment. In both cases the maximum tumor dose was 17.5 Gy. In both of these patients progression to paraparesis ultimately occurred. The mean tumor volume for these six patients with post-SRS tumor progression was 102.6 cm³, 40% greater than the overall mean tumor volume of 61.9 cm³.

Illustrative Cases

Case 1

This 59-year-old woman with RCC had previously undergone 14 fractions of 35 Gy EBRT and had experienced temporary improvement in symptoms. Five months after EBRT she presented with recurrent severe left sacral pain as well as pain and paresthesias radiating into her left leg. A percutaneous fiducial marker was placed 1 week prior to radiosurgery. The radiosurgery plan was designed to treat the tumor with a prescribed dose of 14 Gy that was calculated to the 80% isodose line (Fig. 1). The maximum tumor dose was 17.5 Gy, and the tumor volume was 157 cm³. The spinal canal received a maximum dose of 9.9 Gy. The patient experienced complete pain relief within 1 month, and this was maintained for 30 months. Follow-up imaging has revealed no evidence of tumor progression.

Case 2

This 57-year-old woman harbored T-11 and T-12 RCC metastases. She had undergone surgical treatment of a symptomatic T-6 metastasis resulting in a pathological fracture. At the time of that procedure, fiducial markers were percutaneously implanted. The T-11 and T-12 metastases had not received prior radiation, and these were the only other areas of spinal involvement demonstrated on MR imaging. The intention was to treat these lesions definitively by using primary single-fraction radiosurgery. The patient was neurologically intact. The radiosurgery plan was designed to treat the tumors with a prescribed dose of 18 Gy that was calculated to the 80% isodose line (Fig. 2). The maximum tumor dose was 2.5 Gy, and the tumor volume was 54 cm³. The spinal cord received a maximum dose of 9.8 Gy, and 0.04 cm³ of the spinal cord received greater than 8 Gy. Follow-up MR imaging revealed no evidence of tumor progression at 11 months after CyberKnife treatment, and the patient remains asymptomatic.

Discussion

Despite advances during the past decade in the surgical treatment of patients with localized RCC, 50% of these...
patients initially present with metastases or metastases develop after nephrectomy for Stages I and II tumors. In 30% of patients with RCC spinal metastases will ultimately develop. The spine represents the most common site of osseous involvement for RCC. Standard treatments for RCC metastases to the spine include radiotherapy alone, radiotherapy combined with systemic chemotherapy, or decompressive surgery and/or spinal stabilization followed by radiotherapy. Most patients with RCC metastatic to the spine may be treated by nonoperative measures. The goals of local radiotherapy in the treatment of these spinal tumors have been palliation of pain, prevention of pathological fractures, and cessation of progression or reversal of neurological compromise; however, RCC is a relatively radioresistant tumor and failure to respond to radiotherapy or progressive growth after irradiation is not uncommon. When a spinal tumor causes spinal cord or other neural element compression, decompressive surgery is often necessary with or without the placement of spinal fixation based on the extent of spinal column destruction and spinal instability. Indications for surgery in patients with metastatic spinal disease include intractable pain, spinal instability, or progressive neurological dysfunction secondary to dural compression in cases in which radiotherapy has failed. Patients with extensive osseous destruction of the spinal column should undergo decompressive surgery and stabilization to correct or prevent progressive spinal deformity. Although resection of RCC spinal metastases and stabilization have been shown to improve patients’ neurological function and pain, these lesions are difficult to treat because of their vascularity.

Conventional EBRT for RCC spinal metastases is usually administered in 10 to 20 daily fractions to a total dose of 30 to 40 Gy. A primary factor that limits radiation dose in this conventional radiotherapy is the relatively low tolerance of the spinal cord to radiation. Conventional EBRT is not precise enough to deliver large single-fraction doses of radiation to the spine near radiosensitive structures such as the spinal cord. It is the spinal cord’s low tolerance to radiation that often confines the treatment dose to one that is far below the optimal therapeutic dose. Precise limitation of the radiation dose to the treatment volume, as is the case for intracranial radiosurgery, should maximize the control of RCC spine metastases.

Since Hamilton, et al., first described the possibility of LINAC-based spinal SRS in 1995, investigators at multiple centers have undertaken large-fraction conformal irradiation spinal lesions by using various technologies. Other authors have reported the effectiveness of protons for spinal and paraspinal tumors. In recent studies involving hypofractionated or single-dose treatments for spinal metastases, investigators have reported results that were comparable with those of conventional fractionation. With advances in conformal treatment techniques involving multileaf collimators such as IMRT, Chang, et al., found that intensity-modulated, near-simultaneous, CT scanning–guided stereotactic radiotherapy was a feasible and highly precise modality for the noninvasive treatment of spinal metastases. Bilsky, et al., found successful tumor control in 13 of 15 patients with spinal metastases who underwent IMRT.

Milker-Zabel and colleagues documented tumor control in 95% of their patients. The CyberKnife was first developed for the treatment of benign and malignant intracranial lesions. Treatment outcome has been similar to that associated with conventional frame-based radiosurgery. With the ability to treat lesions outside of the skull via fiducial tracking, CyberKnife treatment of spinal lesions has emerged. Because of the spatial precision with which the CyberKnife can deliver radiation to the spine, it is theoretically feasible to administer a tumoricidal radiation dose in a single fraction similar to that in intracranial radiosurgery.

In SRS, high-dose radiation is delivered in a single fraction to a well-defined intra- or extracranial target. Stereotactic radiosurgery has become an important treatment modality in the management of a wide variety of intracranial and, more recently, extracranial lesions. It has been demonstrated to be an effective treatment for brain metastases, either with or without whole-brain radiotherapy, with an 85 to 95% control rate. The emerging technique involved in spinal radiosurgery represents a logical extension of the current state-of-the-art radiotherapy. Unlike conventional radiotherapy that delivers a full dose to both the VB and the spinal cord, the CyberKnife can deliver a single high-dose fraction of radiation to the target tissue while sparing most of the adjacent spinal cord. The treatment plan can create a high gradient dose falloff to the targeted tissue that should significantly reduce the possibility of radiation-induced myelopathy. This is one advantage of SRS for spinal tumors. It therefore has the potential for significantly improving local control of spinal metastases, which can in turn translate into more effective palliation, delaying progression of neurological deficits requiring open surgical intervention, and potentially leading to longer survival.

There have been no large-scale studies involving spinal radiosurgery or hypofractionated radiotherapy in which their respective optimal doses have been established. At other centers, in which clinicians use intensity-modulated near-simultaneous CT scanning–guided SRS, 6- to 30-Gy doses are delivered in one to five fractions. One difference between our technique and the use of IMRT for conformal spinal radiotherapy is the delivery of the dose in a single fraction rather than in a fractionated treatment scheme. There is simply not enough literature-based evidence regarding the treatment of spinal RCC metastases to allow direct comparison of clinical outcomes obtained using different radiation delivery technologies. Our overall clinical outcomes are similar to those reported by others who have performed hypofractionated radiotherapy. In our series, the maximal tumor dose was maintained at 17.5 to 25 Gy and delivered in a single fraction. Spinal radiosurgery was found to be safe when the doses were comparable with those used in intracranial radiosurgery, without any incidence of radioinduced neural injury. There were no cases of radiation-induced toxicity during a follow-up period of 14 to 48 months (median 37 months), a duration long enough for such events to have occurred.

In this series, pain was the primary indication of radiosurgery treatment. This, of course, is different from the primary indication for intracranial radiosurgery for RCC metastases. Ninety-five percent of patients reported im-
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FIG. 2. Case 1. Axial (left) and sagittal (right) projections of the treatment plan obtained in a 57-year-old woman with T-11 and T-12 RCC metastases. The patient had undergone surgical treatment of a symptomatic T-6 metastasis resulting in a pathological fracture. The T-11 and T-12 metastases had not been previously irradiated and were the only other areas of spinal involvement. The treatment plan was designed with a prescribed dose of 18 Gy to the 80% isodose line. The maximum tumor dose was 22.5 Gy, and the tumor volume was 54 cm$^3$. The spinal cord received a maximum dose of 9.8 Gy, and 0.04 cm$^3$ of the spinal cord received greater than 8 Gy. Note the conformity of the isodose line around the spinal cord.
higher doses to hypoxic portions of the tumor or area of active growth based on functional imaging studies.

One clinical advantage of single-fraction radiosurgery is that the treatment can be completed in a single day rather than over a course of several weeks, which is not inconsequential for patients with a limited life expectancy. The modality may be useful to capitalize on possible advantages of radiosensitizers. In addition, patients with cancer may have difficulty visiting an oncology facility for a prolonged period of daily fractionated therapy. A large single fraction of radiation may be more biologically advantageous in treating certain tumors such as RCC compared with prolonged fractionated radiotherapy. A clinical response such as reduced pain or improved neurological function may also be more rapidly elicited by this form of radiosurgery. Such clinical outcomes are difficult to measure in an outpatient setting. Finally, compared with open surgery the procedure is minimally invasive and can be performed in an outpatient setting. In cases in which the lesions were implanted with fiducials at the time of initial surgery, there is no need to endure the prolonged period normally required for wound healing. Given the negligible dose of radiation to the fascia and skin, radiosurgery can be undertaken without delay soon after open surgery.

Conclusions

In this study with long-term follow-up data, we found that single-fraction spinal SRS for RCC metastases is safe and provides good symptomatic response. The major potential benefits of SRS of spinal lesions are the relatively short treatment time in an outpatient setting, potentially better local tumor control, and minimal risk of side effects. Such factors may translate into better palliation of symptoms and a longer survival period, and the morbidity associated with open surgery of these highly vascular lesions is potentially avoided. In addition, this modality allows for the treatment of lesions previously irradiated using conventional EBRT. This modality offers an important new therapy for spinal RCC metastases. Further experience with higher-dose irradiation and improved tumor imaging will likely lead to even better clinical outcomes.

References

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