Radiosurgery in patients with renal cell carcinoma metastasis to the brain: long-term outcomes and prognostic factors influencing survival and local tumor control

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Object. Renal cell carcinoma is a leading cause of death from cancer and its incidence is increasing. In many patients with renal cell cancer, metastasis to the brain develops at some time during the course of the disease. Corticosteroid therapy, radiotherapy, and resection have been the mainstays of treatment. Nonetheless, the median survival in patients with renal cell carcinoma metastasis is approximately 3 to 6 months. In this study the authors examined the efficacy of gamma knife surgery in treating renal cell carcinoma metastases to the brain and evaluated factors affecting long-term survival.

Methods. The authors conducted a retrospective review of 69 patients undergoing stereotactic radiosurgery for a total of 146 renal cell cancer metastases. Clinical and radiographic data encompassing a 14-year treatment interval were collected. Multivariate analyses were used to determine significant prognostic factors influencing survival.

The overall median length of survival was 15 months (range 1–65 months) from the diagnosis of brain metastasis. After radiosurgery, the median survival was 13 months in patients without and 5 months in those with active extracranial disease. In a multivariate analysis, factors significantly affecting the rate of survival included the following: 1) younger patient age (p = 0.0076); 2) preoperative Karnofsky Performance Scale score (p = 0.0012); 3) time from initial cancer diagnosis to brain metastasis diagnosis (p = 0.0017); 4) treatment dose to the tumor margin (p = 0.0252); 5) maximal treatment dose (p = 0.0127); and 6) treatment isodose (p = 0.0354). Prior tumor resection, chemotherapy, immunotherapy, or whole-brain radiation therapy did not correlate with extended survival.

Postradiosurgical imaging of the brain demonstrated that 63% of the metastases had decreased, 33% remained stable, and 4% eventually increased in size. Two patients (2.9%) later underwent a craniotomy and resection for a tumor refractory to radiosurgery or a new symptomatic metastasis. Eighty-three percent of patients died of progression of extracranial disease.

Conclusions. Stereotactic radiosurgery for treatment of renal cell carcinoma metastases to the brain provides effective local tumor control in approximately 96% of patients and a median length of survival of 15 months. Early detection of brain metastases, aggressive treatment of systemic disease, and a therapeutic strategy including radiosurgery can offer patients an extended survival.

KEY WORDS • metastasis • renal cell carcinoma • gamma knife surgery • radiosurgery

Brain metastasis is the most common type of intracranial tumor. Each year the number of metastatic brain tumors diagnosed by far exceeds the combined total of other intracranial tumors. Renal cell carcinoma accounts for 90% of all primary kidney tumors, and the overall incidence of this cancer is rising for reasons beyond those accounted for by increased use of imaging studies. Four to 17% of patients with renal cell carcinoma develop brain metastasis. Complicating the clinical picture is the fact that more than 50% of patients with renal adenocarcinoma metastatic to the brain either have or will develop multiple lesions. With the advent of improved cancer treatments for extracranial disease, the overall incidence of intracranial metastasis is likely to increase.

Treatment options in patients with brain metastases of renal cell cancer include resection, whole-brain radiation therapy, and symptomatic medical management with corticosteroid agents, all of which lead to a median survival of 4 to 5 months. In patients with renal cell carcinoma, systemic disease and distant metastasis are not uncommon. Because of this, aggressive intervention combined with a low morbidity rate is desirable.

Stereotactic radiosurgery provides, in a single session, a high dose of radiation to a localized brain tumor volume. Brain metastases are frequently easily identifiable as well-demarcated lesions on either CT scans or MR images, and this shape usually makes them amenable to stereotactic radiosurgery.

In this study we detail the efficacy of radiosurgery for treatment of renal cell carcinoma metas-
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tases to the brain and identify factors that correlate with improved survival and local tumor control.

**Clinical Material and Methods**

We reviewed prospectively collected data from all 69 patients with brain metastases of renal cell carcinoma treated with GKS at the University of Pittsburgh between 1987 and 2001. All procedures were performed using gamma knife units (model U, model B, or model C; Elekta Instruments, Atlanta, GA). Usually, an MR imager with a 1.5-tesla magnet was used to obtain images in each patient. The sequences were axial 1-, 2-, or 3-mm slice thickness volume acquisitions with intravenous Gd contrast enhancement. If patients were unable to undergo MR imaging, a CT scan with contrast enhancement was obtained using axial 1-, 2-, or 3-mm contiguous slices throughout the patient’s entire brain. Patients were eligible for radiosurgery if they had between one and four metastases at presentation or one to six metastases that progressed after surgery or fractionated radiation therapy. In addition, no single metastasis in any patient was larger than 3 cm in mean diameter. Both clinical and radiographic data were collected from medical records, national death records, and direct patient follow up, and were entered into a database.

Patients ranged in age from 42 to 83 years (mean age 60 years; Table 1). The sex distribution was 48 male and 21 female patients. The frequency with which the patients underwent GKS was as follows: one time in 69 patients; two times in 13 patients; and three times in three patients. Repeated radiosurgery or external-beam fractionated radiation therapy was performed for new brain metastases. The median time between diagnosis of primary renal cell carcinoma and brain metastasis was 2 months. Preoperative symptoms included seizures (five patients), motor or sensory deficits (37 patients), visual deficits (nine patients), and headaches (13 patients). We noted that 21 patients were neurologically asymptomatic. The median KPS score was 80 (range 50–100). Fifty-seven patients (83%) had active extracranial disease.

Brain metastases were demonstrated on CT scanning or MR imaging. Typically, tumors appeared as contrast-enhancing lesions in the brain parenchyma with surrounding edema. The pathological subtype was usually determined based on diagnosis at the time of resection or biopsy of the primary renal cell carcinoma; however, one patient (1.4%) underwent a stereotactic brain biopsy procedure for confirmation of the histopathological subtype and in 11 patients (16%) confirmation was made during craniotomy and subtotal tumor resection. Thirty-six patients (52%) underwent radiation therapy prior to radiosurgery; the median whole-brain dose was 30 Gy (range 16–40 Gy).

Radiosurgery was performed in a total of 146 tumors. The mean number of tumors per patient was 1.7 (median one; range one–six lesions). Tumor locations in the brain included the following sites: frontal lobe (31 tumors), parietal lobe (39), temporal lobe (18), basal ganglia or thalamus (14), occipital lobe (23), brainstem (five), and cerebellum (16). The amount of radiation was determined and shaped according to the typically irregular morphology in all 146 tumors. One to 12 isocenters (median three isocenters) were targeted during each radiosurgical procedure. The median tumor volume subjected to radiosurgery was 2.8 cm³ (range 0.09–35 cm³). Twenty-nine patients had a tumor volume of less than 2 cm³, and 40 had a tumor volume greater than or equal to 2 cm³. The median dose applied to the tumor margin was 16 Gy (range 12.5–20 Gy). The maximum tumor dose varied from 20 to 40 Gy (median 32 Gy). Dose selection was based on various factors including tumor volume and location, prior radiation therapy, and a predicted dose–response relationship for brain parenchyma necrosis. A representative dose plan is depicted in Fig. 1.

Magnetic resonance imaging, when possible, or CT scanning was performed every 3 months for 1 year and then at 4- to 6-month intervals thereafter. Images were obtained to assess changes in tumor size and the development of new lesions; contrast enhancement defined the tumor margin. A significant change in size was defined as either an increase or a decrease of 2 mm in the outer dimensions (that is, anterior/posterior, right/left, and superior/inferior) of the tumor, compared with its size at the time of radiosurgery.

Survival time was computed both from the time of radiosurgery and from the time of initial diagnosis of renal cell carcinoma metastasis to the brain. Survival curves and the median length of survival were calculated using the Kaplan–Meier method. Factors affecting survival were determined using the Cox proportional hazards model.

**Results**

**Prognostic Factors for Survival**

The overall median survival in this series of 69 patients...
was 15 months (range 1–65 months) from diagnosis of brain metastasis and 6 months (range 1–64 months) from radiosurgery. Overall survival from the time of radiosurgery and from the time of diagnosis of renal cell carcinoma brain metastasis, based on the Kaplan–Meier method, is presented in Fig. 2.

Multivariate testing using the Cox proportional hazards model revealed only six factors that favorably influenced survival (Table 2). These favorable prognostic factors (that is, those with a probability value < 0.05) from the multivariate model included the following: 1) patient age; 2) preoperative KPS score; 3) radiosurgical dose to the tumor margin; 4) maximal radiosurgical dose; 5) treatment isodose; and 6) time from diagnosis of renal cell cancer to the development of brain metastasis. The median length of survival in patients with one brain metastasis and in those with multiple metastases was approximately 15 months from the time of diagnosis of brain metastasis and did not differ in a statistically significant fashion.

We defined active systemic disease as new extracranial metastasis or progression of the primary renal cell cancer. The median length of survival in patients with active systemic disease was 5 months after radiosurgery. In patients without active systemic disease, the median length of survival was 13 months after radiosurgery. The majority of patients (57 [83%]) died of active extracranial disease or from complications associated with primary disease progression. Three patients (4%) were known to have died from progression of their tumor into the central nervous system; the other nine (13%) died of unknown causes.

Prior resection of a brain tumor or fractionated radiation therapy to the brain were evaluated. Although patients who had undergone brain tumor resection (11 [16%]) initially had large tumors, there was no statistically significant difference in the median length of survival in comparing patients with and those without prior resection (p > 0.05, log-rank test). Similarly, the median rate of survival in patients with prior fractionated radiation therapy followed by radiosurgery (36 patients [52%]) and those with radiosurgery alone (33 patients [48%]) was not statistically significantly different (p > 0.05, log-rank test).

Fifty-nine patients died within 24 months after stereotactic radiosurgery (Fig. 2), and 10 patients were alive longer than 24 months after radiosurgery. Five patients lived longer than 3 years, three longer than 4 years, and one lived longer than 5 years after radiosurgery. Two patients (2.9%) underwent a craniotomy and resection after radiosurgery for either intracranial disease progression of a treated tumor or development of a new symptomatic metastasis (one patient each; 1.4%). Seven patients (10%) underwent fractionated radiation therapy after radiosurgery as part of a boost therapy, and eight patients (12%) underwent fractionated radiation therapy after radiosurgery for treatment of new metastasis to the brain demonstrated on neuroimaging.

Fig. 1. Axial, coronal, and sagittal MR images comprising a radiosurgical dose plan for the treatment of renal cell carcinoma metastasis to the brain. The respective isodose curves are denoted by numbers on the dose plan.
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Local Tumor Control

Radiosurgery was undertaken to treat 146 tumors in 69 patients. Postradiosurgical imaging (either MR imaging or CT scanning) was used to evaluate 76 of these tumors. Tumor size was measured in anterior/posterior, right/left, and superior/inferior dimensions and the results were compared with dimensions measured from images obtained at the time of stereotactic dose planning. Images of the remaining tumors were not obtained, either because of early patient death from systemic disease or their failure to comply with imaging follow up.

Local tumor control was achieved in 73 (96%) of 76 tumors evaluated and in 94% of patients who underwent imaging follow up (Table 3). A representative response to radiosurgery is exhibited in Fig. 3. Forty-nine new metastases were noted in 27 patients (39%). Sixteen of these patients (23% of the total number) underwent repeated radiosurgery for treatment of the new metastasis. Eight patients (12%) underwent fractionated radiation for new brain metastasis, and one (1.4%) underwent resection for a brain metastasis that proved refractory to both radiosurgery and fractionated radiation therapy.

Complications in Patients

Three patients (4.3%) had worsening peritumoral edema demonstrated on follow-up imaging; symptomatic edema was treated with a short course of corticosteroid agents. In one patient (1.4%) intratumoral hemorrhage was evident on postradiosurgical imaging, and this individual died shortly after radiosurgery as a result of the hemorrhage. Three patients (4.3%) exhibited radiographic evidence of progression of tumors previously treated with radiosurgery.

Discussion

Brain metastases represent the most common type of intracranial tumors based on both neuroimaging and autopsy studies. In patients with renal cell cancer, brain metas-
tasis frequently occurs, between 4 and 17% of the time. If untreated, the median survival time in patients with brain metastases is a dismal 1 to 2 months. Fractionated radiation therapy has increased the median length of survival to 3 to 6 months. Most radiation oncology centers use doses of 30 to 40 Gy, delivered in 10 to 20 fractions. In the present series of patients with renal cell cancer, 30 patients (43%) received radiation therapy prior to radiosurgery, and an additional 15 patients (22%) received radiation therapy after radiosurgery. Nonetheless, there was no statistically significant difference in survival between patients who did and those who did not receive fractionated radiation therapy.

Resection is an important part of the neurosurgical armamentarium for the treatment of brain metastases. Excision of a metastasis is generally recommended if the lesion is large, surrounded by much edema, symptomatic, and accessible. Patients slated for surgery tend to be a highly select group because individuals with this disease often cannot undergo resection of the metastasis due to its location in the brain, significant extracranial disease, and the presence of multiple, symptomatic tumors. Authors of recent series in which resection was combined with fractionated radiation therapy reported median survival times of 10 to 14 months, although data published on such patients are limited. In a randomized trial in which investigators had compared the combination of fractionated radiation therapy and resection (median survival 5.6 months) with radiation therapy alone (median survival 6.3 months), no statistically significant difference in survival was demonstrated. Note that the median length of survival in surgically treated patients with multiple tumors was worse at 6 months. In two series of patients with brain metastasis of renal cell carcinoma who had undergone surgery, operative mortality rates varied between 9 and 10% and postoperative complication rates were 28%. Moreover, the local tumor control rate reported by Badalament, et al., was 85% compared with 96% in our series of patients. Surgical outcomes were best in patients with solitary, accessible tumors and in patients with no active systemic disease.

In the present radiosurgical series, eleven patients (16%) had undergone prior resection of a renal cell carcinoma metastasis to the brain, but resection did not correlate with increased survival. This may be a result of the fact that patients in our series had radiographically demonstrated tumor recurrence after surgery. With radiosurgery, no treatment-related mortality occurred. The number of metastases did not correlate with survival. Radiosurgery can be used to treat multiple, widely separated, and surgically inaccessible brain metastases in a single session.

Chemotherapy and immunotherapy generally are ineffective for the management of intracranial metastasis from renal cell carcinoma. These modalities remain the mainstay for treatment of systemic disease, but reported response rates vary between 5 and 20%. Because most patients with metastatic cancer to the brain in this series and in others are dying of systemic disease progression, chemotherapy and immunotherapy are important in the overall treatment of extracranial disease in patients with metastatic renal cell carcinoma.

With brain metastasis, the goals of radiosurgery are localized tumor control, improvement of clinical symptoms, prolongation of survival, and low morbidity and mortality rates. Data in the present series demonstrate median sur-

<table>
<thead>
<tr>
<th>Radiological Response</th>
<th>Value (%)</th>
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<tbody>
<tr>
<td>decrease in size</td>
<td>48 (63)</td>
</tr>
<tr>
<td>size unchanged</td>
<td>25 (33)</td>
</tr>
<tr>
<td>increase in size</td>
<td>3 (4)</td>
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<tr>
<td>delayed tumor hemorrhage</td>
<td>1 (1.4% of all patients)</td>
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<tr>
<td>delayed distant brain metastases</td>
<td>.49 (39% of all patients)</td>
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vivals of 15 months after diagnosis of brain metastasis and 6 months after radiosurgery. These survival results are comparable to those of smaller series in which patients with brain metastasis of renal cell carcinoma were treated radiosurgically.2,6,22,25,33,35,40,45,47,52,55 Death from intracranial disease progression was far less common (4%) than that from extracranial disease progression (83%). Although late, distant metastasis to the brain occurred in 39% of patients, development of new intracranial metastasis was not the cause of death, except in one patient.

Local tumor control rates in patients treated radiosurgically for renal cell carcinoma metastasis to the brain vary from 85 to 100%.2,6,22,25,40,47 In the current study, a tumor control rate of 96% was achieved. Although renal cell carcinoma metastasis to the brain has been regarded as more resistant to conventional radiation therapy, it consistently appears to be amenable to radiosurgical treatment.24,28 The majority of researchers report applying a radiosurgical dose ranging from 15 to 30 Gy to the tumor margin.2,6,22,25,34,45,47 In the present study, the median doses to the tumor margin and its center were 16 and 32 Gy, respectively. Results of multivariate analysis revealed that higher tumor margin and maximal doses were statistically related to improved median survival. In selecting a radiosurgical dose, one must strike a balance between an amount that is sufficient to achieve local tumor control and one that would cause radiation-induced parenchymal injury.18 Also, a higher treatment isodose correlated with improved survival, which may be related to the fact that higher treatment isodoses were sometimes used in tighter and better defined radiosurgical treatment planning.

Rationale for Radiosurgery

Metastatic renal cell cancer is well suited for radiosurgery because lesions are typically small (<3 cm in greatest dimension), approximately spherical in shape, and enhance well on MR images or CT scans. Radiosurgery for these lesions is intended to provide local tumor control, to stabilize or improve clinical symptomatology, and to enhance survival. All of these radiosurgical goals are generally achieved with low morbidity, low cost, and essentially zero mortality.37,43,48 In fact, data from recent radiosurgical series have consistently demonstrated a favorable quality of life in the majority of patients treated with GKS.2,13,50,56

In North America, patients with multiple metastases and often those with only a solitary metastasis are traditionally referred for fractionated radiation therapy first. Patients with inactive systemic disease and those with a large, solitary, symptomatic brain metastasis in a surgically amenable location undergo resection. At the University of Pittsburgh, radiosurgery is performed in patients with the following conditions: 1) patients with one to four brain metastases in locations not amenable to resection (for example, deeper brain structures, brainstem, and so on); 2) patients who have undergone fractionated radiation therapy but who demonstrate growth of at least one tumor or the presence of new or persistent tumors afterward; and 3) patients who have undergone prior resection and demonstrate residual tumor or recurrence on follow-up imaging.

After radiosurgery, each patient should be followed up both clinically and radiographically. Radiographic follow-up entails obtaining serial, contrast-enhanced MR images or contrast-enhanced CT scans if an MR image is contraindicated in a particular patient. In either case, thin-sectioned axial and coronal scans should be obtained to detect changes in tumor dimensions and to evaluate for the presence of new metastases. Given the 4 to 17% incidence of brain metastases in patients with renal cell cancer and the ease with which imaging of the brain can be performed, screening imaging of the brain may prove useful in detecting metastases that are small and asymptomatic. It remains to be seen whether early detection and treatment of brain metastases with radiosurgery will lead to improved survival.

Historically, patients with renal cell carcinoma metastases to the brain frequently died as a result of intracranial disease progression. Renal cell carcinoma metastases were often considered less sensitive to conventional radiation therapy; however, 83% of patients in the present radiosurgical series died from extracranial disease progression or with known active systemic disease. As more patients with active extracranial disease are referred, the overall median length of survival will decrease. In a previous report, median survival was 11 months after radiosurgery.35 In the present series, however, the percent of patients with active extracranial disease increased from 74% in the previous report to 83%. In this series, only 4% of patients died of intracranial disease progression and 13% died of unknown causes. Because of this, the overall management of these patients requires a multimodal approach, with a perspective beyond a patient’s intracranial disease. A goal of prolonged survival in patients with intracranial disease may prompt more aggressive treatment of both the primary and other extracranial sites of metastatic disease.

Conclusions

Gamma knife surgery appears to be effective in treating renal cell carcinoma metastases to the brain. Primary treatment of brain metastases with radiosurgery can enhance patient survival and facilitate local tumor control. Moreover, it does so with low morbidity and essentially zero mortality rates. Radiosurgery can also lead to local tumor control in patients who have not benefited from resection or radiation therapy. In determining the status of a patient with renal cell cancer, imaging of the brain may reveal small (that is, <3 cm in diameter) and even asymptomatic lesions well suited for radiosurgery. Early radiosurgery combined with aggressive therapies to treat extracranial disease will, we hope, lead to prolonged survival and a better quality of life.

Disclaimer

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References

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