Multidisciplinary Treatment of Brain Metastases Derived From Clear Cell Renal Cancer Incorporating Stereotactic Radiosurgery

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BACKGROUND. Brain metastases are a frequent complication in patients with metastatic clear cell renal cancer. Survival after whole-brain radiotherapy (WBRT) is disappointing. A retrospective analysis of multimodality treatment was performed in patients who had received linear accelerator (LINAC)-based stereotactic radiosurgery (SRS).

METHODS. Thirty-two patients underwent SRS-based treatment for 71 metastatic foci between 2000 and 2006. All patients had a Karnofsky performance status $\geq$70 and all 32 patients had extracranial metastatic disease (Radiation Therapy Oncology Group recursive partitioning analysis [RPA] Class 2). Survival was calculated from the time of diagnosis of brain metastases. The minimum potential follow-up was 1 year after SRS. Univariate and multivariate analysis of potential prognostic factors affecting survival was performed.

RESULTS. Twenty-six patients required only 1 SRS treatment (84%) to achieve central nervous system (CNS) control, whereas 5 patients received 2 to 3 treatments (16%). The median survival of renal cancer patients from the diagnosis of brain metastases was 10.1 months (95% confidence interval, 6.4-14.8 months). One-year and 3-year survival rates were 43% and 16%, respectively. The addition of surgery or WBRT did not appear to prolong survival. Immunotherapy after control of brain metastases with SRS appeared to result in significantly improved survival. Survival was also found to be strongly influenced by prognostic stratification of metastatic disease using Motzer or modified risk criteria.

CONCLUSIONS. The results of the current study demonstrated that SRS-based treatment of patients with up to 5 brain metastases from clear cell renal cancer is feasible and results in excellent CNS control. Survival beyond 3 years from the time of diagnosis of brain metastases was achievable in 16% of patients and was associated with the use of systemic immunotherapy with interleukin-2 and interferon but not antiangiogenic agents. ***Cancer* 2008;113:2539–48.** © *2008 American Cancer Society.*

KEYWORDS: renal cancer, renal cell carcinoma, brain metastases, stereotactic radiosurgery, immunotherapy, interleukin-2, interferon.

Renal cancer frequently metastasizes to the brain. A 5% to 10% incidence of brain metastases has been reported in renal cancer patients.[1] The percentage of all renal cancer patients who eventually develop brain involvement (also termed incidence proportion percentage) is also surprisingly high (6.5%). This ranks third among all tumor types, exceeded only by lung cancer and melanoma.[2]

A decade ago the survival of patients who developed brain metastases from renal cancer was typically quite short, with a median of 4 to 7 months.[3,4] Surgical resection, usually in combination with radiotherapy, can achieve long-term survival in a small percentage

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of these patients, particularly those with only 1 or 2 superficial lesions in the absence of extracranial metastases.[5] Unfortunately, the majority of patients with brain metastases from renal cancer are not surgical candidates. Whole-brain radiotherapy (WBRT), therefore, has been the standard palliative treatment. For example, Wronski et al[3] reported treatment results of 119 patients treated for renal cancer brain metastases with WBRT. The median survival with 1 brain metastasis (49 patients) was 4.4 months. If multiple brain metastases were present (70 patients), the median survival decreased to 3.0 months. Greater than 76% of patients in this series died because of central nervous system (CNS) progression.

In recent years there have been numerous reports of a high response rate, durable local control, and apparently prolonged survival after stereotactic radiosurgery (SRS) of brain metastases derived from renal cancer using either linear accelerator (LINAC) or gamma-knife-based treatment approaches.[6-22] We hypothesized that further improvement can be obtained by a multidisciplinary treatment approach, encompassing aggressive LINAC-based SRS treatment of brain metastases and subsequent systemic therapy for extracranial disease.

MATERIALS AND METHODS

Patient Selection

After Institutional Review Board approval, we performed a retrospective review of patients with clear cell renal cancer and brain metastases who were treated with an SRS-based approach. We identified 32 patients with renal carcinoma with brain metastases who were treated with SRS between March 2000 and December 2006 from institutional records.

Clinical information obtained on these 32 patients included age, sex, original American Joint Committee on Cancer (AJCC) stage of disease, date of initial renal cell carcinoma diagnosis, date of extracranial metastases, date of diagnosis of brain metastases, number of brain metastases, treatment of CNS disease (surgical or WBRT), date of SRS, number of SRS treatments, radiation dose administered by SRS, radiation dose administered by WBRT, local control of SRS targeted lesions, and date of CNS progression.

The type of systemic treatment administered and the date of systemic disease progression were extracted from the medical record. Whether patients received immunotherapy (interferon or interleukin-2 [IL-2]) or antiangiogenic treatment (bevacizumab, sorafenib, sunitinib, or thalidomide) was specifically noted.

Prognostic Stratification

The natural history of renal cancer is quite variable, making interpretation of treatment outcome difficult. To analyze whether known prognostic indicators influenced the outcome of patients with brain metastases, patients were assigned to good, intermediate, and poor prognostic groups based on Motzer risk classification at the time of their original diagnosis.[23] Clinical information, including normalized calcium level >10 mg/dL, anemia, Karnofsky performance status (KPS) $<80\%$, lack of prior nephrectomy, and lactate dehydrogenase (LDH) $>1.5\times$ normal, was ascertained from the medical record. The good prognosis group was defined as having 0 risk factors, the intermediate risk group had 1 to 2 risk factors, and the poor risk group had ≥ 3 risk factors.

Patients were also stratified using 'modified risk criteria' that added the number of organ systems (≥ 2) involved with metastases and the development of metastatic disease within 1 year from the time of initial diagnosis in addition to 4 of the Motzer risk factors (hypercalcemia, anemia, KPS $<80\%$, and elevated LDH).[24] In this prognostic scheme, the favorable prognosis group had no or 1 risk factor, the intermediate-risk group had 2 risk factors, and the poor-risk group had ≥ 3 risk factors.

Clinical Management Strategy

All patients with stage IV renal cell carcinoma were screened with a brain magnetic resonance imaging scan at the time of initial evaluation. Follow-up brain imaging was performed if warranted by development of neurologic symptoms. Patients were aggressively treated if brain metastases were identified, using SRS as the primary treatment modality if there were ≤ 5 brain metastases. WBRT was usually used if >5 brain lesions were present, with stereotactic boost to all large lesions. SRS-treated patients were followed with brain imaging studies at least every 2 months to 3 months and salvage treatment with additional SRS or WBRT was attempted if there was radiographic evidence of disease progression. Palliative surgery was performed if there was a surgically accessible dominant symptomatic lesion.

SRS Planning and Treatment

Brain metastases were treated with LINAC-based SRS as previously described.[25] The treatment dose was prescribed to the isodose line covering 95% of the target volume (range, 80%-97%). The planned dose was based on the maximal dimension of each metastatic lesion: <2 cm, 20 grays (Gy)to 24 Gy; 2 to 3 cm, 18 Gy; and 3 to 4 cm, 15 Gy, based on Radiation Therapy Oncology Group (RTOG) protocol 9508.[26] In

general, lesions measuring ≥4 cm in dimension were not treated with SRS.

Systemic Therapy

All 32 patients had extracranial metastases from renal cancer. Twenty-three of 32 patients in the current series received subsequent systemic therapy at our institution. All were considered for high-dose intravenous IL-2 treatment.[27] Fourteen patients received high-dose IL-2 treatment, 7 of them after SRS treatment of brain metastases. An additional 3 patients had received low-dose subcutaneous IL-2 before referral. Interferon-α was administered to 6 patients before the development of CNS metastases and to an additional 3 patients after SRS treatment. Six patients were treated with both agents. One patient was followed without therapy after SRS because of personal choice. Eight patients had been referred for SRS from other institutions and did not receive systemic treatment at our institution.

Antiangiogenic compounds were preferentially used as part of clinical trials. Bevacizumab, at a dose of 10 mg/kg intravenously every 2 weeks, was administered to 13 patients, including 10 who received it after SRS. Sunitinib (SU11248), given at a dose of 50 mg daily orally for 4 weeks on/2 weeks off, was administered to 6 patients, 4 of them after SRS. Sorafenib, administered at a dose of 400 mg orally twice daily, was given to 5 patients, including 3 who received it after SRS treatment. Thalidomide was administered to 2 patients, both after SRS treatment. The response of systemic disease was assessed with computed tomography scans every 2 to 3 months.

Statistical Analysis

Overall survival using the Kaplan-Meier method was the primary endpoint of this retrospective analysis.[28] Survival was defined as the time (in months) from the diagnosis of brain metastases until death or last clinical follow-up. Survival from the diagnosis of metastatic extracranial disease for patients who developed late brain progression was also calculated. The log-rank test was used to calculate *P* values.[29]

Secondary outcomes included evaluation of local control of the treated lesion by SRS, overall CNS control, and type of progression (CNS, systemic, or both). Cox proportional hazards regression analysis was used to explore the effects of sex, added WBRT, neurosurgery, initial number of brain metastases (1 vs ≥2), prognostic stratification, and systemic treatment with immunotherapy or antiangiogenic agents on overall survival and CNS progression.[30] All 32 patients were included in the univariate and multivariate analysis of prognostic factors (including treatment effect), even though 8 patients did not receive systemic therapy at the study institution (none had received high-dose IL-2 at another institution). Twenty patients were included in analysis of time to CNS progression after brain metastases. Statistical significance was established at a probability level of <.05. Statistical analysis was performed using Statistica 6.0 software (StatSoft, Tulsa, Okla) and R 2.4.1 (R-Foundation for Statistical Computing, Vienna, Austria).

TABLE 1
Patient Characteristics

	No. of Patients
Gender	25 men (78%), 7 women (22%)
Median age, y	63 (range, 46-79)
Median time from original diagnosis, y	3.4 (range, 0-21)
No. of brain metastases	
1	14 (44%)
2-15	18 (56%)
No. of SRS treatments	
1	27 (84%)
2-3	5 (16%)
WBRT	12 (38%)
Neurosurgery	11 (35%)
Immunotherapy	19 (59%)
Antiangiogenic therapy	16 (50%)

SRS indicates stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

RESULTS

Characterization of Patient Population

From March 2000 to December 2006, 32 patients with 71 intracranial metastases from clear cell renal cancer were diagnosed and treated with SRS (Table 1). At the time of initial diagnosis, 4 patients presented with stage I disease, 3 patients had stage III disease, and the rest (25 patients) already had stage IV disease. Five patients (16%) had synchronous brain metastases at the time of original diagnosis of stage IV renal cancer. Fourteen patients had only a solitary brain metastasis, whereas 18 had ≥2 metastases (range, 2-15 metastases). All patients had active extracranial metastases at the time they developed brain metastases.

Outcome of SRS-based Treatment

The tumor volume of SRS-treated brain metastases ranged from 0.03 to 26.9 cm^3. Transient adverse effects included facial edema and ecchymoses from head frame application. Two patients developed symptomatic radiation necrosis of a brain metastasis requiring palliative neurosurgical resection. Both

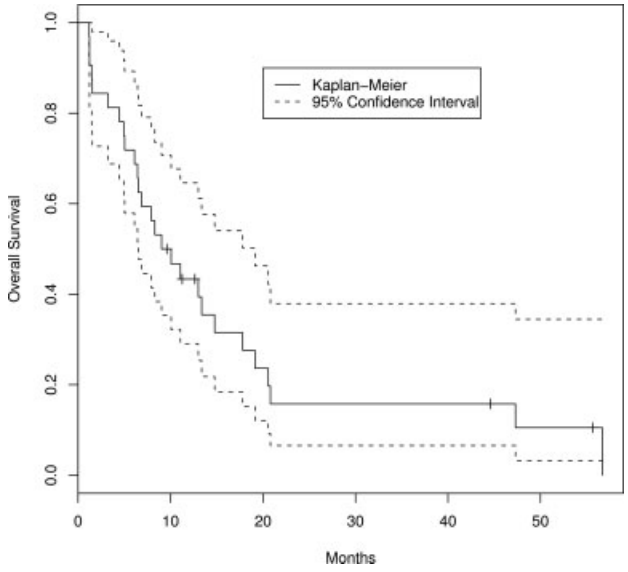

FIGURE 1. Overall survival of patients with clear cell renal cancer from the time of diagnosis of brain metastases (95% confidence interval is shown by dotted lines).

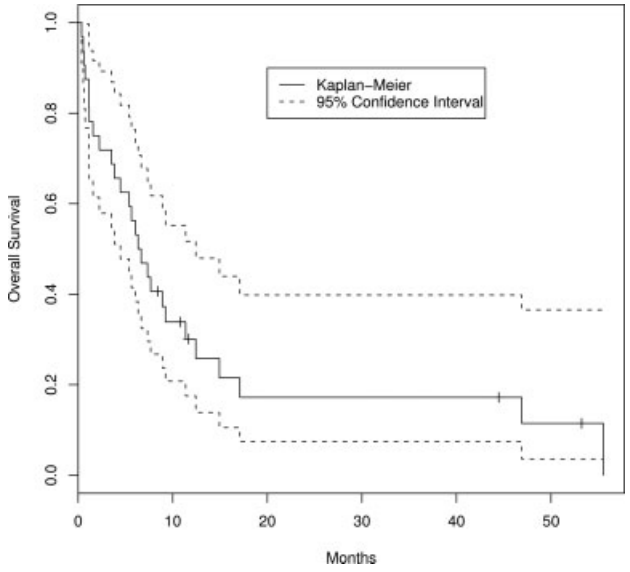

FIGURE 2. Overall survival of patients with clear cell renal cancer from the time of stereotactic radiosurgery (95% confidence interval is shown by dotted lines).

patients had been treated with sequential SRS and WBRT. A ventriculoperitoneal shunt was required in a third patient because of ventricular entrapment. This most likely represented a tumor-related complication.

Only a single SRS treatment was required to achieve CNS control in 27 patients (84%), whereas 5 patients received 2 SRS treatments (16%). Failure was generally because of the development of new metastases that could be treated for salvage with additional SRS or WBRT. In the entire group of patients, there was a CNS control rate of 60% at 1 year and 32% at 2 years. The median survival from the time of the diagnosis of brain metastases was 10.1 months (95% confidence interval [95% CI], 6.4-14.8 months) (Fig. 1). The median survival from SRS was 6.7 months (95% CI, 3.8-11.4 months) (Fig. 2). The 1-year and 3-year survival rates from the onset of brain metastases were 43% and 16%, respectively. Six patients remained alive without CNS progression with follow-up ranging from 9.6 to 55.7 months (median, 17.8 months) from the time of diagnosis of brain metastases. The number of brain metastases (range, 1-5 metastases) treated with SRS did not appear to significantly influence survival. Fourteen patients with a single brain metastases had a median survival of 8.9 months compared with 5.4 months for the 18 patients with multiple metastases ($P = .19$).

Local control data were available for 22 patients and for 42 of 71 treated brain metastases. There were 6 local failures among the SRS-treated metastases. The probability of local control in treated lesions was 86%, 74%, and 59%, respectively, at 1 year, 2 years, and 3 years after SRS. Overall disease control in the CNS was achieved in 16 of 20 (80%) of fully evaluable patients and in 42 (91%) of evaluable lesions with a single SRS treatment. Only 8 of 22 patients eventually developed new brain metastases; all were in association with extracranial tumor progression. The median time to CNS progression of any treated lesion after SRS was 15 months (95% CI, 8.7 months-∞).

Twenty-nine patients were treated for newly diagnosed brain metastases and 3 developed progressive disease after WBRT and received salvage SRS. Five of 29 newly diagnosed patients received WBRT as part of their initial planned treatment, whereas 24 received initial SRS alone. Only 4 (16.7%) of the patients treated with initial SRS ever required WBRT. Survival did not appear to be altered by addition of WBRT or neurosurgery.

Evaluation of Known Prognostic Factors

Patient outcome was analyzed based on known prognostic factors for renal carcinoma without brain metastases using the Motzer classification,[31] as well as modified risk criteria.[24] From the time of diagnosis of metastatic disease (before the development of brain metastases in the majority of patients), both prognostic schemes accurately stratified overall survival (Table 2). Motzer and modified risk criteria demonstrated survival of 50.9 months and 59.5 months, respectively, in the good-prognosis group;

TABLE 2
Prognostic Factors and Survival From the Time of Initial Diagnosis of Metastatic Disease

Classification	No. of Patients	Median Survival, Months	95% CI, Months	*P*
Motzer classification				
Good	13 (42%)	50.9	35.7-∞	
Intermediate	15 (48%)	26.1	19.4-∞	
Poor	3 (10%)	3.9	1.2-∞	$<10^{-10}$
Modified risk criteria				
Good	16 (52%)	59.5	35.7-∞	
Intermediate	8 (26%)	26.0	12.8-∞	
Poor	7 (22%)	8.3	3.9-∞	.0002

95% CI indicates 95% confidence interval.

TABLE 3
Survival From the Time of Initial SRS Treatment Stratified by Prognostic Classification

Classification	No. of Patients	Median Survival, Months	95% CI, Months	*P*
Motzer classification				
Good	13 (42%)	7.7	6.3-∞	
Intermediate	15 (48%)	6.1	2.2-∞	
Poor	3 (10%)	0.9	0.4-∞	.002
Modified risk criteria				
Good	16 (50%)	8.9	6.7-∞	
Intermediate	8 (25%)	4.9	1.6-∞	
Poor	8 (25%)	1.7	1.1-∞	.012

SRS indicates stereotactic radiosurgery; 95% CI, 95% confidence interval.

26.1 months and 26 months, respectively, in the intermediate-prognosis group; and 3.9 months and 8.3 months, respectively, in the poor-prognosis group (Motzer, $P < 10^{-10}$; modified risk criteria, $P = .0002$).

Survival from the time of CNS metastases for the group of patients with a good prognosis was 7.7 months and 8.9 months, respectively, by Motzer and modified risk criteria (Table 3). In the intermediate-prognosis group, survival was 6.1 months and 4.9 months, respectively, and was 0.9 months and 1.7 months, respectively, for the poor-prognosis group ($P = .002$ for the Motzer classification and $P = .012$ for modified risk criteria) (Fig. 3).

Role of Systemic Therapy

Systemic immunotherapy with interferon-α or IL-2 was administered to 19 patients. Fourteen patients received high-dose IL-2, 7 of them after SRS treatment of brain metastases. Patients received on average 1.8 cycles (range, 1-4 cycles) of high-dose IL-2. An additional 3 patients had received prior treatment with low-dose, subcutaneous IL-2 elsewhere before the onset of CNS metastases. Nine patients received interferon-α, 3 of them after SRS treatment. Six patients received both IL-2 and interferon.

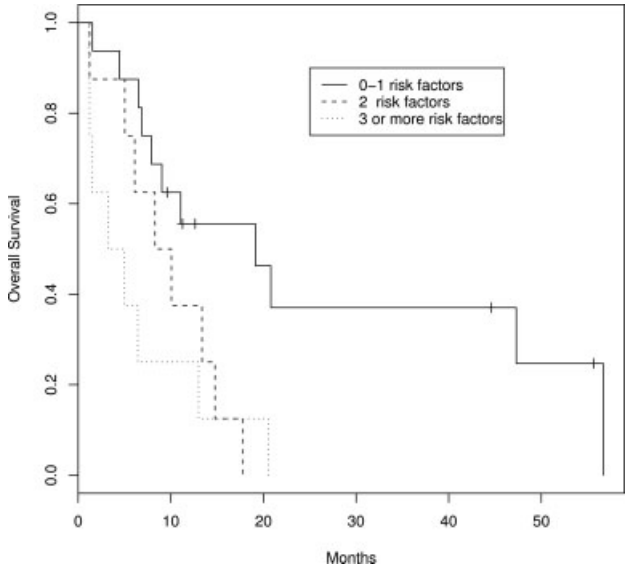

FIGURE 3. Survival of patients with renal cancer brain metastases stratified by modified risk criteria into good-risk, intermediate-risk, and poor-risk groups at the time of diagnosis of metastatic disease.

Survival for all patients who ever received systemic immunotherapy (either before or after the treatment of brain metastases) was 6.1 months versus 7.3 months for those who did not ($P = .13$). However, when patients who received immunotherapy after the completion of SRS were compared with those who did not (Fig. 4), there was a substantial survival benefit (17.1 months vs 5.4 months) noted ($P = .0007$). The median time to CNS progression in these immunotherapy patients was also prolonged at 23.2 months, compared with the 5 patients who did not receive immunotherapy, who had a median time to CNS progression of 15 months ($P = .07$).

Of the 16 patients receiving treatment with antiangiogenic agents, 13 received them after SRS. It should be noted that none of the 13 developed vascular adverse events (ie, congestive heart failure, ischemic stroke, or intracranial hemorrhage). Nine patients received 1 antiangiogenic agent; 5 patients were treated with 2 sequential agents; and 2 patients received sorafenib, bevacizumab, and sunitinib sequentially. Although anecdotal CNS responses have been reported with antiangiogenesis agents, patients in the current series who received treatment with antiangiogenic agents at any time during the course

of their disease did not have a significantly improved survival (8.3 months vs 4.9 months; $P = .35$).

Analysis of Potential Risk Factors Using Univariate and Multivariate Analysis

On univariate analysis (Table 4), the use of neurosurgery, WBRT, systemic treatment (pooled) after SRS treatment of brain metastases, antiangiogenic therapy (bevacizumab, sunitinib, sorafenib, or thalidomide), or the number of CNS lesions (1 vs $\geq$2 metastases) did not appear to affect survival. The administration of immunotherapy after SRS appeared to significantly prolong survival ($P = .0007$). A significant component of this effect appeared to be because of IL-2 treatment after SRS ($P = .04$). Multivariate Cox regression analysis tested the effect of systemic therapy after SRS on survival after brain metastases, after adjusting for risk factors. Survival of patients with brain metastases who were treated with immunotherapy after SRS remained highly significant in combination with stratification by known prognostic factors (Motzer, $P = .0023$; and modified risk criteria, $P = .0011$) (Table 5). Multivariate analysis also demonstrated that survival was significantly improved in patients receiving high-dose IL-2 treatment after SRS when stratified by modified risk criteria ($P = .009$) but not Motzer criteria ($P = .11$). Patients with only a single brain metastasis who received immunotherapy after SRS treatment also demonstrated a trend toward improved survival when stratified by either prognostic scheme ($P = .07$). It is notable that only 1 patient with single SRS-treated metastasis eventually progressed within the CNS after subsequent immunotherapy, compared with 7 of 10 patients (median time to recurrence of 8.7 months) who had $\geq$2 SRS-treated lesions and were then treated with immunotherapy ($P = .07$).

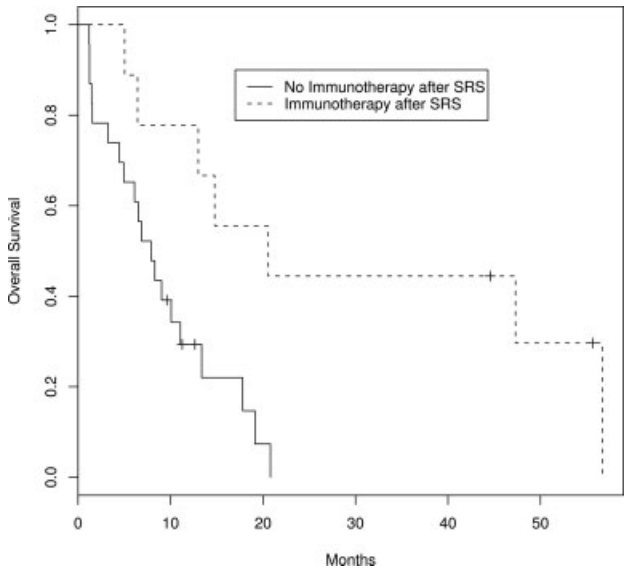

FIGURE 4. Survival of patients with brain metastases from clear cell renal cancer who received immunotherapy with interleukin-2 or interferon after stereotactic radiosurgery (SRS).

The characteristics of long-term survivors are shown in Table 6. Several observations are suggested. Benefit was most frequently noted after IL-2 therapy (administered after SRS for brain metastases). Although objective responses were reported, 'stable disease' patients also appeared to benefit, in association with long periods of tumor growth arrest. It should be noted that objective responses (as determined by Response Evaluation Criteria in Solid Tumors [RECIST]) criteria are rare after SRS of brain metastases, with the majority of patients having a best response of 'stable disease' on brain magnetic resonance imaging (MRI). This affects scoring of objective response overall. Two of the patients in the current study were alive at the time of last follow-up, 1 with gradual progression of disease after

TABLE 4
Univariate Analysis of Survival in Patients With CNS Metastases From Renal Cancer

Characteristic	Group 1 (No.)	Median Survival (95% CI)	Group 2 (No.)	Median Survival (95% CI)	*P*
Gender	Male (25)	6.3 (3.8-11)	Female (7)	12.4 (1.2-∞)	.84
CNS lesions	Single (14)	8.1 (6.3-∞)	$\geq$ 2 (18)	4.9 (1.2-∞)	.19
Neurosurgery	Yes (11)	7.7 (5.6-∞)	No (21)	6.3 (1.2-∞)	.33
WBRT	Yes (12)	7.5 (4.5-∞)	No (20)	6.2 (3.5-∞)	.95
Antiangiogenic agent	Yes (16)	8.3 (6.1-∞)	No (16)	4.9 (1.1-∞)	.35
Antiangiogenic agent after SRS	Yes (13)	9.2 (6.3-∞)	No (19)	4.5 (1.2-∞)	.13
Immunotherapy	Yes (19)	6.1 (4.5-∞)	No (13)	7.3 (1.1-∞)	.50
Immunotherapy after SRS	Yes (9)	17.1 (6.1-∞)	No (23)	5.4 (1.6-9.2)	.0007
IL-2 after SRS	Yes (7)	17.1 (6.1-∞)	No (25)	5.6 (2.2-∞)	.04

CNS indicates central nervous system; 95% CI, 95% confidence interval; WBRT, whole-brain radiotherapy; SRS, stereotactic radiosurgery; IL-2, interleukin-2.

immunotherapy failure, with subsequent sequential response to multiple vascular endothelial growth factor (VEGF) pathway inhibiting agents. One patient had a CNS-only recurrence after an IL-2-induced complete response. This was salvaged with additional SRS. This patient remained free of disease at the time of last follow-up.

DISCUSSION

Brain metastases are a frequent and devastating complication in 5% to 10% of patients with metastatic renal cancer, even with short-term follow-up.[1] The risk of brain metastases in the current series was found to be higher in men (3.6:1 male:female ratio). The majority of patients who developed brain metastases presented with stage IV disease at the time of initial diagnosis. Brain metastases also were correlated with active extracranial metastatic disease (all patients in the curent series). Brain metastases were generally detected late, a median 3.4 years from the time of diagnosis of metastatic renal cancer, similar to other reports.[5] Nevertheless, a 16% incidence of synchronous brain metastases was found at the time of initial diagnosis of metastatic disease.

TABLE 5
Multivariate Analysis of Survival After Treatment of Brain Metastases: Impact of Immunotherapy

Prognostic Factors	*P*
Immunotherapy and Motzer criteria after SRS	.0023
Immunotherapy and modified risk criteria after SRS	.0011
IL-2 treatment and Motzer criteria after SRS	.11
IL-2 treatment and modified risk criteria after SRS	.009

SRS indicates stereotactic radiosurgery; IL-2, interleukin-2.

Historically, neurosurgery, usually in combination with radiotherapy, has provided the best hope of long-term survival for a small percentage of renal cancer patients with brain metastases.[5] Patients most likely to benefit from surgery currently generally have 1 to 2 surgically accessible and asymptomatic lesions, excellent performance status, and the absence of extracranial metastases. Because the majority of patients are believed to be unresectable at the time of presentation, WBRT has become the de facto standard of care for patients with brain metastases from renal cancer. Performance status and Radiation Therapy Oncology Group recursive partitioning analysis (RPA) class are important determinants of survival after WBRT.[32] Unfortunately, survival of WBRT-treated patients is short (median, 4-7 months).[3,4] Therefore, it has been suggested that brain metastases from renal cancer are 'radioresistant.'[33,34]

SRS, using either LINAC-based or gamma-knife technology, can achieve higher radiation doses within a small tumor volume. In published series of patients with brain metastases from renal cancer, SRS has produced a high response rate, durable local control, and apparently prolonged survival.[6-22] Similar outcomes have been reported using either LINAC-based or gamma-knife-based treatment approaches. Eligibility has generally been limited to patients with 1 to 3 small metastases, with rare series accepting patients with larger numbers of lesions.[35,36] Recent studies have also found that the outcome of SRS or neurosurgical resection plus WBRT for lesions measuring $\leq$2 cm appears to be similar.[37,38] We have shown that excellent outcome can be obtained by expanding eligibility to patients with up to 5 brain metastases and adding subsequent systemic therapy to control extracranial disease.

In the current study patients, excellent local control of each brain metastases was achieved by SRS.

TABLE 6
Characteristics of Long-term Responders Treated With SRS Followed by Subsequent Immunotherapy

Age, Years	Gender	Organ Systems Involved	Immunotherapy	Best Response to Immunotherapy	Subsequent Antiangiogenic Treatment	Time to Disease Progression, Years	Survival From Onset of Metastatic RCC	Site of Eventual Disease Progression	WBRT Added,
72	Man	5	Interferon	SD	Bevacizumab	4	9.1	Systemic + CNS	No
55	Man	6	IL-2	PD	—	4.5	8.2	Systemic + CNS	Yes
46	Man	2	IL-2	CR	—	4.8	5.3+	CNS only	Yes
52	Man	2	IL-2	SD	Bevacizumab, sunitinib, and sorafenib	3	5.2+	Systemic + CNS	No
74	Woman	5	IL-2	SD	Sunitinib	1.33	2.2	Systemic	No

SRS indicates stereotactic radiosurgery; RCC, renal cell cancer; WBRT, whole-brain radiotherapy; SD, stable disease; CNS, central nervous system; IL-2, interleukin-2; PD, progressive disease; CR, complete response.

Twenty-six patients required only a single SRS treatment (84%) to achieve CNS control, whereas 5 patients received 2 treatments (16%). The overall CNS control rate remained 60% at 1 year and 32% at 2 years. Failures generally related to the development of new lesions, rather than progression at treated sites. In general, salvage treatment with additional SRS (for $\leq$5 lesions) or WBRT (for $>$5 lesions) was successfully used to treat new lesions.

Overall survival from the onset of metastatic disease in the current series was 26.6 months (95% CI, 22.7-58.7 months) with 1-year and 2-year survival rates of 80% and 63%, respectively. This survival is remarkably long, and appears to reflect general improvement in the survival of metastatic renal cancer patients over the last 3 years. The 1-year and 2-year survival rates from the onset of brain metastases were 33% and 16%, respectively, with some protracted progression-free survivors (16% at $>$3 years).

Survival in metastatic renal cancer is strongly influenced by definable patient prognostic factors.[23] It was not previously known whether these prognostic factors apply to patients who develop brain metastases because this finding may further worsen prognosis. In the patients in the current study, both the Motzer and modified risk criteria (assigned at the time of the original diagnosis of metastatic disease) were found to be strongly correlated with overall survival, despite the later development of brain metastases. This finding implies that the underlying tumor biology reflected by these risk criteria has an overriding influence on outcome.

We performed a multivariate analysis to explore potential risk factors that may influence patient outcome. Our results extend these observations, suggesting that systemic immunotherapy with interferon-α or IL-2 after SRS may be safely administered after the treatment of brain metastases and may markedly increase survival for a subset of patients. Guirguis et al[39] previously reported the results of IL-2 treatment in the small number of patients with brain metastases treated at the National Cancer Institute (NCI) Surgery Branch. There was no significant difference in IL-2 toxicity or in reasons for stopping IL-2 administration noted between patients with or without CNS involvement. Patients with previously treated brain metastases demonstrated an 18.5% objective response to IL-2 treatment, compared with patients with untreated brain metastases (5.6% response rate) and patients without brain involvement (19.8%). Those authors concluded that carefully selected patients with brain metastases can safely receive high-dose IL-2, and some can respond at intracranial and extracranial disease sites. These exploratory observations should encourage further evaluation of IL-2-based treatment in patients with adequately treated brain metastases.

Of 16 patients receiving treatment with antiangiogenic agents, 13 safely received them after SRS. Although anecdotal CNS responses have been reported with antiangiogenesis agents (eg, sunitinib), there has also been a suggestion of increased incidence of brain hemorrhage, particularly if brain metastases were not treated first.[40] None of the patients in the current study had an objective response to antiangiogenic treatment on MRI scans. Survival appeared to be minimally influenced by the use of antiangiogenic therapy, but because of the small sample size, this observation will require additional confirmation.

There is currently controversy regarding the precise role and optimum sequence of SRS and WBRT for the treatment of brain metastases. The addition of SRS to WBRT (compared with WBRT alone) appears to be beneficial, across a variety of tumor types.[26,41] In contrast, the results of SRS with or without planned immediate WBRT are less clearcut.[42] The 12-month brain metastases recurrence rate was lower in the WBRT + SRS group (including only 8% renal cancer patients). Salvage brain treatment was also less frequently required in the WBRT + SRS group. However, death attributed to neurologic causes occurred in a similar number of patients (22.8% in the WBRT + SRS group vs 19.3% in the SRS-only group; $P = .64$) and there was no difference in overall survival noted between the 2 groups ($P = .42$). The concept of delaying or omitting WBRT was further supported (at least in selected patients) by the Eastern Cooperative Oncology Group (ECOG) 6397 study.[34] The results of the current study indicate that excellent CNS control of renal cancer brain metastases can be achieved for the majority of patients using SRS as the primary treatment modality, without immediate WBRT. It appears likely that SRS of renal cancer brain metastases with delayed WBRT will result in survival similar to that of SRS with immediate WBRT in metastatic renal cancer patients. Because of the small and retrospective nature of the current study, these results will need to be confirmed in a prospective clinical trial. A prospective trial could also better characterize which patient subsets benefit from SRS-based treatment (eg, Motzer poor-risk patients appear to have very short survival despite SRS in our experience, and therefore may gain minimal benefit from SRS-based treatment). Critical evaluation of quality of life and survival endpoints will also need to be performed.

It should be emphasized that all patients treated for brain metastases, including those treated with

primary SRS for brain metastases, require close follow-up, because some will eventually develop disease progression in the CNS. We, and others, have shown that SRS, as well as surgery or WBRT, can be used as effective salvage therapy. A significant percentage of renal cancer patients with brain metastases, especially those with solitary lesions and 0 to 1 adverse risk factors, can achieve long-term, disease-free survival with SRS followed by subsequent immunotherapy. The role of IL-2 in producing long-term disease control in these patients is intriguing.

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