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Radiosurgery

Stereotactic radiosurgery as single-modality treatment of incidentally identified renal cell carcinoma brain metastases ☆

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Abstract

Background: Initial staging evaluation of patients with renal cell carcinoma (RCC) has led increasingly to the diagnosis of brain metastases in patients who are otherwise neurologically asymptomatic. We present our experience treating patients with incidentally identified brain metastases with initial stereotactic radiosurgery (SRS) monotherapy and compare outcomes with those of patients treated at our institution with other strategies and with those reported in the literature.

Methods: We conducted a retrospective outcomes analysis in patients with incidentally identified RCC brain metastasis treated with initial SRS monotherapy. Our radiation oncology and tumor databases were reviewed, identifying 80 patients treated between 1990 and 2006.

Results: We found 19 patients with asymptomatic, incidentally identified brain metastasis (KPS, 90-100) treated with SRS monotherapy within 60 days of diagnosis. Stereotactic radiosurgery was performed at a mean of 17.8 days from diagnosis to an average of 3.1 lesions (range, 3-11; mean lesion volume, 1.72 cm^3; mean total volume, 4.53 cm^3). The mean prescription was 21.3 Gy delivered to the mean 59.97% isodose line. The mean survival for these patients was 21.5 months (median, 12.6 months) and was not statistically different from survival in similar patients treated with other therapeutic modalities. Local control was achieved in 95% of patients; distant central nervous system progression occurred in 79% of patients at a mean of 450 days.

Conclusions: We demonstrate that patients with incidentally identified RCC brain metastases treated with initial SRS monotherapy achieved a survival rate comparable with that of patients managed with standard therapeutic modalities. Our findings suggest that SRS alone is an attractive therapeutic option for patients with incidentally identified brain metastases from RCC.

Keywords: Renal cell carcinoma; Stereotactic radiosurgery; Radiation; Survival; Performance score; Recursive partitioning analysis

Abbreviations: cGy, centigray; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Score; RCC, renal cell carcinoma; RPA, recursive partitioning analysis; RTOG, Radiation Therapy Oncology Group; SRS, stereotactic radiosurgery; WBI, whole brain irradiation; WBRT, whole brain radiotherapy

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1. Introduction

Each year, 30 000 new cases of RCC are diagnosed [17]; 60% of these patients will develop metastatic disease [34]. Approximately 4% to 17% of metastatic RCCs involve the brain [32], for an estimated incidence of 1200 to 5100 cases annually. Most of the brain lesions are clinically asymptomatic [31] and are discovered during routine staging evaluation; such cases pose a unique therapeutic challenge. Because effective treatment of brain metastases can improve both quality of life and outcomes in selected patients, as well as influence eligibility for clinical trials, patients stand to benefit from early, aggressive control of their CNS disease. Conversely, the benefits of early treatment of brain metastases must be weighed against the delays that such interventions, particularly those associated with surgery or whole brain irradiation (WBI), may cause for the management of the primary malignancy; and so, strategies must maximize CNS control and minimize delays in systemic therapy.

Optimal management of brain metastasis has not been defined and generally must be conducted on an individual basis. Essentially all clinical studies reported involve symptomatic patients. The median survival of patients with untreated RCC brain metastases averages 3 to 4 months [9]. Monotherapy with WBI confers benefit in many patients, with median survival of 8.5, 3.0, and 0.6 months for RPA (Table 1) class 1, 2, and 3 patients, respectively, [5]. Surgical resection of RCC brain metastases has resulted in reported mean survival times ranging from 2.5 to 27.5 months [25,29,35]. These data must be viewed with caution, however, as selection bias toward patients with good performance status, limited systemic disease, and only a single metastasis may influence these results. Surgery and adjuvant WBI, which decreases recurrence and improves survival in patients with metastatic brain lesions, are generally applied in concert [27].

The modest response of RCC brain metastases to WBI alone has traditionally been considered the result of a "relatively radioresistant" phenotype. Current thinking suggests that this resistance may be a dose-dependent outcome, and RCC lesions may be effectively treated with higher radiation doses [4,10,11]. Until the advent of SRS, however, the clinical significance of this distinction was limited by the radiosensitivity of the normal brain. Overall survival for patients undergoing monotherapy with SRS has been reported at 7.5 to 12.5 months [6,15,19,28,30,33]; and survival stratified by RPA class has been reported at 18 to 24, 8.5 to 9.2, and 5.3 to 7.5 months for classes 1, 2, and 3, respectively [14,23]. Furthermore, local control rates lie in the 80% to 98% range [4,22-24,33]. Adding WBI to SRS may not improve either overall survival or local or distant recurrence rates [1,2,12,13,16,22].

Although not directly comparable, these studies suggest that survival is similar when RCC brain metastases are managed either with SRS or with surgery and WBI. In general, most patients with metastatic tumors, including RCC, die of complications related to their primary malignancy or to additional, distant CNS metastases. Neither the major study of WBI with or without SRS (RTOG 9508) nor a recent randomized trial of SRS with or without WBI included significant numbers of patients with RCC (4/331 and 10/132 patients, respectively), so the optimal method of managing RCC metastases to the brain remains unclear [1,2]. Finally, neither study examined asymptomatic patients, a significant proportion of RCC patients (as many as 86% of patients may have minimal or no neurologic symptoms at the time of diagnosis [31]); and the number of patients with brain metastasis, symptomatic or not, may likely grow, as an increasing number of patients with metastases outside the CNS survive because of improved control with newer, molecularly targeted agents [7].

Stereotactic radiosurgery is an attractive option to patients with incidentally discovered RCC brain metastases, as it combines the potential for definitive or extended local control with a favorable adverse effect profile, a brief recovery period, and minimal delay of treatment of the primary malignancy and may be repeated or have WBI added subsequently. Because of the inherent limitations of the RPA system, specific outcomes data for such patients are lacking. We analyzed the outcomes of patients with incidentally discovered RCC brain metastases who were managed initially with SRS monotherapy.

Table 1
Recursive partitioning analysis class definitions

RPA class	Description
I	Age <65 y KPS ≥70 Primary disease controlled No systemic disease
II	KPS ≥70 and 1 of the following: Age ≥65 y Uncontrolled or synchronous primary disease Systemic disease
III	KPS <70

2. Materials and methods

2.1. Patient selection

Patients who were diagnosed with RCC and had one or more brain lesions consistent with metastases were eligible for inclusion in this study. For the purpose of this retrospective study, asymptomatic was defined as a Karnofsky Performance Score (KPS) greater than or equal to 90 and no neurologic symptoms or signs related to the brain lesion(s); patients with a KPS of 80 or lower were excluded. Patients younger than 18 years at the time of diagnosis; patients who harbored more than one active, primary malignancy of different histologic type; or patients for whom inadequate clinical information was available to collect the necessary data were also excluded from the analysis. Between 1990 and 2004, 80 patients were identified who fit these criteria. Data were extracted, compiled, and verified against patients' archived medical records. The Social Security Death Index was used to verify dates of death when necessary. The Cleveland Clinic Institutional Review Board approved this study.

2.2. Identifying patients managed with initial SRS monotherapy

Initial treatment with SRS monotherapy was defined as (1) SRS within 60 days of diagnosis of brain metastases and (2) no other therapy for the CNS lesions (whole brain radiotherapy [WBRT], surgery) either before or within 60 days after completion of initial SRS therapy. Stereotactic radiosurgery was performed on an outpatient basis using the gamma knife (Elekta model B [1997-2002] or Elekta model C [2002-2004]). Treatment of recurrent or progressive CNS disease with surgery, WBRT, or SRS occurring 61 or more days after initial SRS therapy was considered salvage therapy; and patients receiving such treatments were included in the analysis. A total of 19 patients satisfied these criteria and comprised the study group.

2.3. Identifying similar patients managed with other therapeutic modalities

To compare the results of patients managed with SRS only with similar patients managed with other therapeutic modalities, the RCC patients enrolled between 1990 and 2005 with RCC, one or more brain metastases, and KPS greater than or equal to 90. Subsets of patients were identified who received WBI only, surgery only, WBI + surgery, or WBI + SRS. For each group, patients received (1) the identified modality within 60 days of diagnosis of brain metastases and (2) no other therapy for the CNS lesions either before or within 60 days of completion of initial therapy. Treatment of recurrent or progressive CNS disease with surgery, WBRT, or SRS occurring 61 or more days after initial therapy was again considered salvage therapy; and patients receiving such treatments were included in the analysis. A total of 17 patients fit these criteria, representing patients treated with standard modalities. The therapy these patients received was dictated by their treating physicians, which reflects current clinical practice.

2.4. Statistical methods

Survival time was computed as the number of months between initial imaging diagnosis of brain metastases and death. Time to treatment was defined as the number of days between imaging diagnosis of brain metastases and initial therapy for these lesions. Patients believed to be alive at the time of data analysis had a censored survival point entered, which was defined as the date from which the last documented piece of clinical evidence was available to verify patient survival. Mean and median values, standard deviations, and confidence intervals (CIs) were computed in the standard fashion. A heteroscedastic, 2-tailed Student t test was used to compare survival between therapeutic groups. Comparisons were considered to be statistically significant for P less than .05.

3. Results

3.1. Dosimetry analysis

Dosimetry data were analyzed for all patients receiving radiotherapy to verify uniform treatment within the study groups and concordance with standard accepted therapeutic dosages. Patients in the SRS-only group received a mean prescribed dose of 21.3 Gy (95% CI, ±3.81 Gy) delivered to the mean 59.96% (95% CI, ±3.39%) isodose line. Patients treated with WBRT only received a mean total dose of 35 Gy (95% CI, ±0.35 Gy) with a mean fractionated dose of 262.5 cGy (95% CI, ±24.5 cGy). Patients treated with WBRT + SRS received a mean total WBRT dose of 33.8 Gy (95% CI, ±0.42 Gy) with a mean fractionated dose of 275 cGy (95% CI, ±28.3 cGy) (data not available for 1 of 5 patients) and a mean SRS dose of 19.6 Gy (95% CI, ±3.66 Gy) prescribed to the mean 55% (95% CI, ±5.07) isodose line. Data were available for 1 of the 2 patients treated with WBRT + surgery, who received 30 Gy with a fractionated dose of 300 cGy. The differences in mean prescribed dose and isodose line between the SRS-only group and SRS + WBRT group were not statistically significant (P = .41 and P = .15). The differences in mean total WBRT dose and mean fraction WBRT dose between the SRS + WBRT group and the WBRT-only group were not statistically significant (P = .67). The availability of data from only 1 of 2 patients in the WBRT + surgery group precludes such analysis. Data regarding precise lesion volume are generally not recorded for patients treated with modalities other than SRS, but the mean number of lesions treated in the SRS group (3.1) was not significantly different from the mean number of lesions in patients treated with alternate modalities (2.2, P = .23).

3.2. SRS treatment group

Nineteen patients with incidentally discovered brain metastasis were managed with initial SRS monotherapy. The group was 78% male and 22% female. The mean age at diagnosis was 58.7 years (95% CI, ±4.95 years), and the median KPS was 90. Patients presented with a mean of 3.11 (95% CI, ±1.24) brain lesions with a mean lesion volume of 1.72 cm^3 (95% CI, ±1.07 cm^3). A total of 59 lesions in 19 patients were treated, 44 (75%) of these being supratentorial, 6 (10%) infratentorial, and 9 (15%) intraventricular and/or originating in the choroid plexus. Eight patients (42%) had metastatic disease outside of the CNS at the time of diagnosis, with metastases to a mean of 1.25 additional organs. Based upon age (5 patients >65 years), extracranial metastatic disease (n = 8), and/or uncontrolled primary disease (n = 7), 18 of 19 patients were assigned to RPA class 2 at the time of diagnosis. All patients had undergone or were actively

Table 2
Demographics of the 19 patients with incidentally diagnosed brain metastases from RCC

No. of patients	19
Male/female	15 (79%)/4 (21%)
Age at diagnosis (mean)	58.7 y [±4.95]
KPS at diagnosis	
Patients with KPS = 90 (n)	11
Patients with KPS = 100 (n)	8
Median KPS	90
Time to GK (diagnosis of metastases to therapy)	17.8 d [±6.13]
Total no. of brain lesions treated	59
No. of brain lesions (mean)	3.11 [±1.24]
Lesion volume (mean)	1.72 cm^3 [±1.07]
Lesion location	
Supratentorial	44 (75%)
Infratentorial	6 (10%)
Intraventricular/choroid plexus	9 (15%)
RPA class at diagnosis	
Class 1	1 (5%)
Class 2	18 (95%)
CNS progression after SRS	
No. of patients achieving local control	18 (95%)
No. of patients with progression of treated lesion	1 (5%)
Time to progression (mean)	210 d
No. developing additional (distant) brain metastases	14 (73%)
Time to progression (mean)	450.0 d [±332.8]
No. of additional brain lesions (after initial SRS, mean)	2.37 [±0.97]
Total patients developing CNS progression	15 (79%)
Systemic progression	
No. of patients with systemic progression	18 [95%]
Time to progression (mean)	1087 d [±678.45]
Cause of death	
Systemic progression of primary malignancy	12 (63%)
Distant brain/CNS progression	5 (26%)
Unclear/unknown	2 (11%)
Survival (mean)	21.46 mo [±10.08]
Survival (median)	12.58 mo

Brackets indicate 95% CIs.

undergoing standard medical therapy for their primary malignancy at the time of SRS. Stereotactic radiosurgery was performed a mean of 17.84 days (95% CI, ±6.13 days) from diagnosis of CNS metastases.

Eighteen patients (95%) achieved local control (growth arrest or resolution of treated lesion[s]), whereas 1 patient (5%) developed local progression of his CNS disease 210 days after initial SRS. Fourteen patients (74%) developed a mean of 2.37 (95% CI, ±0.97) additional, distant CNS lesions throughout the remainder of their lives, with the first new lesion(s) being diagnosed at a mean of 450.0 days (95% CI, ±332.84 days) from initial diagnosis of brain metastases. Overall, a total of 15 patients (79%) experienced some form of CNS progression (1 local, 14 distant). All patients with progressive CNS disease underwent one or more rounds of salvage therapy. Of these 15 patients, 4 received salvage WBRT, 6 had repeated SRS, 1 underwent surgery, and 4 were treated with a combination of 2 or more modalities. Eighteen patients (95%) experienced systemic progression of their disease at a mean of 1087.0 days (95% CI, ±678.45 days) after initial diagnosis of their primary malignancy.

The mean survival for patients who received initial SRS monotherapy for their incidentally discovered brain metastases was 21.46 months (95% CI, ±10.08 months), and the median was 12.58 months. These data are summarized in Table 2.

3.3. Alternate-modality treatment groups

To investigate the possible effects of lead time bias, survival data were collected for similar patients initially treated with WBRT only, WBRT + SRS, surgery only, and surgery + WBRT. The mean survival for patients treated with WBRT monotherapy was 18.77 months (95% CI, ±14.92 months; median, 14.92 months). The mean survival for patients treated with WBRT + SRS was 5.30 months (95% CI, ±1.81 months; median, 4.24 months). The mean survival for patients treated with surgery only was 34.25 months (95% CI, ±36.87 months; median, 34.25 months). The mean survival for patients treated with surgery + WBRT was 17.51 months (95% CI, ±22.47 months; median, 17.51 months). Only the relative decrease in mean survival of the SRS + WBRT group was statistically significant when compared with the mean survival of patients treated with upfront SRS monotherapy. The wide CIs for the mean survival calculated for these groups are likely attributable to the small sample size in each group, which is considered in the discussion below. We also attempted to compensate for this effect by constructing a composite group containing all patients with

Table 3
Outcomes in patients treated with various strategies (including all RPA classes)

	SRS	WBRT	SRS + WBRT	Surgery	Surgery + WBRT	All modalities except initial SRS monotherapy
No. of patients	19	4	5	2	2	17
Mean survival (mo)	21.46	18.77	5.30	34.25	17.51	15.87
Median survival (mo)	12.58	14.54	4.24	34.25	17.51	8.71
95% CI	10.08	14.92	1.81	36.87	22.47	7.09
t test (vs SRS only)		0.78	0.01	0.62	0.79	0.38
t test (vs WBRT only)			0.17	0.56	0.94	0.75
t test (vs SRS + WBRT)				0.37	0.48	0.01
t test (vs surgery)					0.93	0.97
t test (vs surgery + WBRT)						0.91

Table 4
Outcomes in patients treated with various strategies (RPA class 2 only)

	Initial SRS monotherapy, all RPA classes	Initial SRS only, RPA class 2 only	All modalities except initial SRS monotherapy, RPA class 2 only
No. of patients	19	18	14
Mean survival (mo)	21.46	16.15	14.10
Median survival (mo)	12.58	11.71	7.82
95% CI	10.08	9.11	6.48
t test (vs SRS-monotherapy group)		0.45	0.24
t test (vs SRS-monotherapy group, RPA class 2 only)			0.72

KPS greater than or equal to 90 (n = 17) treated with any modality other than initial SRS monotherapy and comparing outcomes for this group with those of the SRS-monotherapy group. The mean survival for patients in this composite group was 15.87 months (95% CI, ±7.09 months; median, 8.71 months). The difference in mean survival vs the SRS-monotherapy group was not significant. The results of this analysis are presented in Table 3.

3.4. Limiting group comparisons by RPA class

Most patients treated initially with SRS monotherapy were RPA class 2 at the time of diagnosis (18 of 19, 95%). This was also true for patients treated with alternate therapeutic modalities. However, to further standardize the comparisons with published literature, we compared outcomes after subtracting RPA class 1 patients from the SRS-monotherapy group and from the composite group of patients treated with alternate therapeutic modalities. The mean survival was 16.15 months (95% CI, ±9.11 months; median, 11.71 months) and 14.10 months (95% CI, ±6.48 months; median, 7.82 months), respectively. The mean survival difference between groups was not significant (Table 4). Too few RPA class 1 patients were available to facilitate meaningful comparisons limited to patients in this class.

4. Discussion

4.1. Outcomes after SRS for incidentally discovered brain metastases

Imaging of the neuraxis is becoming routine at many institutions as a part of initial staging workup for patients presenting with newly diagnosed RCC. Up to 86% of these patients may harbor clinically asymptomatic brain metastasis, generating the need for a management strategy for patients with incidentally discovered tumors [31]. At the time of diagnosis of their CNS disease, these patients often undergo local or systemic therapy for their newly diagnosed primary tumors and have concerns related to both optimal medical management and quality of life. This clinical scenario makes SRS an attractive option, as it combines proven efficacy and potential for definitive, local control with a favorable adverse effect profile, a brief recovery period, and minimal or no delay in treating the primary malignancy.

Current literature suggests that SRS monotherapy is a viable treatment of RCC brain metastasis. It provides local control and confers survival benefits comparable with those associated with more invasive interventions. Because of the relatively low incidence of RCC brain metastasis, however, initial outcomes research in these patients necessitated analysis of clinically heterogeneous groups to achieve adequate sample size. More recently, this issue has been addressed by analyzing outcomes in patients stratified by RPA class; and these data reaffirm the role of SRS in selected patients with RCC metastasis. One limitation of the RPA classification system is that it lacks the ability to separate patients with moderate neurologic deficits (KPS ≤80) from patients who have normal function and are likely neurologically intact (KPS ≥90). Patients in the latter group are often wary of potential cognitive adverse effects of WBRT [8,26] and are eager to avoid major surgery, if possible, as they are about to begin or are actively undergoing therapy for their primary malignancy. Stereotactic radiosurgery presents an attractive option, but outcome data for this growing patient population have thus far been unavailable.

We have analyzed outcome data for neurologically asymptomatic patients treated with initial SRS monotherapy for brain metastases from RCC. Analysis of the demographic information of the patients in our study group indicates that they typically present with 3 brain metastases with an average tumor volume of 1.72 cm^3. These patients achieve excellent local control after SRS, with only 5% experiencing local progression. This rate is comparable with recurrence data reported elsewhere [4,22-24,33]. Mean survival for this patient group is 21.46 ± 10.08 months. Most patients died from systemic progression (n = 12, 63%), but a minority died of distant progression of CNS disease (n = 5, 26%). The cause of death could not be accurately assessed in 2 patients (11%).

4.2. Comparison of outcomes data

The mean survival of 21.5 months seen in this series of patients with incidentally identified RCC brain metastases is at least 8 months longer than the mean documented survival of the overall population of patients with RCC brain metastases undergoing similar treatment (7.5-12.5 months) [25,29,35]. This effect is again demonstrated when the comparison is limited to RPA class 2 patients in each group, where the mean survivals are 16.1 months and 8.5 to 9.2

months, respectively. One possible explanation for this observation is that earlier intervention with SRS improves overall survival. However, local control rates that approach 95% when SRS is used in both the overall population of patients with RCC brain metastases and in the subset with incidentally discovered lesions suggest that the timing of SRS may be only one source of the efficacy of this modality in these groups. Instead, we believe that the additional 8 months of survival may represent a lead time effect introduced by the emerging practice of empiric screening of the neuraxis during routine staging workups for RCC in patients before the development of significant neurologic symptoms, likely when lesions are smaller.

To correct for this effect and to compare outcomes of SRS with those of other therapeutic modalities used in this subgroup, we analyzed survival in patients with similar, incidentally discovered CNS metastases from RCC primaries who were treated with different therapeutic strategies. Because SRS is the most common intervention used at our institution when patients present with this clinical scenario, however, a total of only 17 such patients were identified in the same treatment period. There was no statistical difference in the mean overall survival of this group of 17 patients compared with the mean survival of the study group ($P = .38$). This suggests that survival after SRS in patients with incidentally discovered RCC brain metastases is comparable with survival achieved with other modalities, independent of the lead time effect.

The group of 17 patients was divided into subgroups of patients managed with WBRT monotherapy, surgery, surgery + WBRT, or SRS + WBRT. This resulted in low sample numbers in each group, limiting the ability to compare the calculated survival in these groups with those of the study group or with those published in the literature. We calculated outcomes for these groups despite the low sample numbers, and only the mean survival of the SRS + WBRT group differed significantly from the mean survival of the study group. Retrospective review of the 2 patients in this group demonstrated that therapy was undertaken for palliation rather than for cure in both. This again suggests that survival after SRS in patients with incidentally discovered RCC brain metastases is comparable with survival observed with other therapeutic modalities, although we caution against overanalysis of this data given the small sample size in each group.

4.3. SRS vs surgery as initial monotherapy in patients with incidentally discovered RCC brain metastasis

The median survival after initial surgical resection of RCC brain metastases is documented in the literature as 12.5 to 27.5 months [25,29,35]. This is comparable with the median survival of 12.6 months (mean, 21.5 months) that we have reported when patients with incidentally discovered lesions are treated with initial SRS monotherapy, even if the possible effects of an 8-month potential lead time effect are subtracted. In addition, the survival rates reported after surgery are influenced by selection biases that favor inclusion restricted to patients with solitary, superficial, easily resectable lesions at the expense of patients with multiple or deeper metastases [25,29,35]. This effect is minimized in our study group because location and multiplicity were not factors that precluded SRS. Finally, although factors such as perioperative morbidity, length of hospital stay, and delay of treatment of the primary malignancy are not specifically analyzed in either study, all are presumably less in patients undergoing SRS compared with those undergoing craniotomy. We therefore conclude that there is no evidence supporting craniotomy over SRS in this patient population, and there is at least some suggestion that the opposite may be true.

4.4. Sample size

One limitation of this study is the relatively small sample size of the study group ($n = 19$). Although we agree that larger samples are desirable, it is important to consider that RCC metastases comprise only a small fraction of the total population of CNS metastases treated at neurooncology centers. In the prospective trial of Aoyama et al [2] of WBRT vs SRS, only 10 (7.5%) of 132 patients had primary RCC. Five of these patients were treated with SRS, and outcomes data from these patients were combined with data from the remaining 92.5% of the experimental population into the final statistical analysis. A larger study by ECOG focusing on renal, melanoma, and sarcoma metastases had a somewhat larger RCC cohort, with 14 patients enrolled [20]. Here, we have analyzed outcomes after SRS monotherapy in a specific subset of the already limited group of patients with RCC brain metastases and have generated data specific to this unique clinical subpopulation. Review of over 14 years of clinical data allowed us to identify and to study outcomes in a cohort nearly 4 times larger than the SRS-treated RCC subgroup in the trial of Aoyama et al. When viewed in this light, we believe that the sample size is both understandable and reasonable. Collection of a larger data set would require a much more extensive, multicenter, prospective effort.

4.5. Comparison groups

We recognize that this is a retrospective study of specific subgroups of patients with RCC and brain metastases managed with one of several possible strategies. Just as the relatively low prevalence of such patients explains the small sample population (see above), it also explains why only limited outcomes data are available regarding similar patients treated with alternate strategies. We recognize that the comparison groups that we have presented each have small numbers of patients, and we have been careful not to draw overly broad conclusions from the statistical analyses performed. This study was designed to highlight the outcomes in the experimental population, which suggest that SRS alone is a reasonable management strategy in such patients. The comparison groups are presented to highlight the fact that there is little consensus regarding the ideal management strategies for such patients and to present our experience with the management of these patients. Rather than omitting the limited data for the alternate-modality groups, we have chosen to present all of the outcomes data that we have gathered for these patients to offer readers the benefit of our complete experience. Ultimately, large-scale, randomized, prospective trials will be necessary to identify an ideal management strategy for RCC brain metastases.

4.6. Cognitive outcomes

Cognitive outcome in treated patients is a complex issue reflecting both the treatments and the tumor and can be difficult to unravel. Although it could not be studied in further detail in this retrospective analysis, it is rightly becoming a critical issue in most prospective and consortium studies of all brain tumors, primary and metastatic [18,21]. In the post hoc analysis of Aoyama et al [3] of patient data in their study of WBRT vs WBRT + SRS, they found that tumor control was a major factor for stabilizing neurocognitive function and that local control rates were better for patients treated with SRS + WBRT (88.7%) and for patients treated with SRS alone (72.5%). Similar results regarding local control were demonstrated by ECOG in their investigation of patients with renal cell, melanoma, and sarcoma metastases [20].

Our study focused exclusively on patients with incidentally identified RCC brain metastases treated with SRS monotherapy. We have observed a local control rate of 95% in such patients, which is better than the 72.5% observed in the analysis of Aoyama et al [2] of patients managed with SRS monotherapy and which more closely approximates the local control of the cohort treated with SRS + WBRT in that study. Because patients with RCC were poorly represented in the investigations of Aoyama et al (n = 10, 7.5%) and were not analyzed as a unique subgroup, it is unclear if this reflects a statistical effect attributable to sample size or increasing survival attributable to new systemic chemotherapeutics for RCC, or if it reflects real differences in underlying biology or response to therapy. We highlight this finding because of emerging evidence of the importance of tumor control [3,20] and its correlation with cognitive outcomes [3], but we caution that our study was not designed or powered for direct statistical comparison with these prospective trials.

4.7. Summary

This study represents a first attempt to review a unique problem—how to manage an asymptomatic RCC brain metastasis—one that will likely increase with improved systemic therapies and widespread use of scanning patients at presentation, similar to patients with small cell lung cancer. Our results suggest that SRS monotherapy, administered following standard RTOG dosimetry guidelines for the treatment of intracranial metastases, may be an acceptable treatment strategy for patients with incidentally identified RCC brain metastases. The retrospective nature of this investigation and the limited size of the experimental and comparison populations mean that further investigation is necessary before stronger conclusions can be drawn. Ideally, this should be performed in the setting of prospective, multicenter studies.

4.8. Implications for clinical practice

Our outcomes analysis demonstrates that patients with incidentally discovered RCC brain metastasis treated with initial SRS monotherapy have survival comparable with that of patients treated with other accepted therapeutic strategies. Assuming that they are otherwise appropriate SRS candidates, these patients may receive survival benefits comparable with those conferred by WBRT and/or surgery without assuming whatever potential risks and adverse effects may be associated with those treatment modalities. In addition, SRS can generally be performed promptly and with minimal recovery time, minimizing disruption in the treatment plan for the primary malignancy in newly diagnosed RCC patients, who comprise a significant proportion of patients at our center. We believe that these findings support SRS as a viable therapeutic option for selected patients in this group.

5. Conclusions

Patients presenting with incidentally discovered brain metastases from RCC primary tumors managed with SRS have a mean survival of 21.46 ± 10.08 months (median, 12.58 months). This is at least comparable with survival after treatment with surgery ± WBRT. Stereotactic radiosurgery therefore represents a potential alternative to other therapeutic modalities for patients with incidentally discovered RCC brain metastases, as it confers comparable survival benefits without some of the risks and adverse effects that may be associated with alternate treatment modalities. This is particularly important to patients who present in this fashion, who generally wish to minimize potential cognitive adverse effects, avoid surgery if possible, and expedite treatment of their primary malignancy. Thus, for small-volume, asymptomatic RCC brain metastases, SRS provides comparable long-term local control and survival with alternate therapeutic strategies. Central nervous system relapse, local or distant, may still be treated by repeated SRS, WBI, craniotomy, or a combination of these modalities. Larger-scale, prospective clinical trials are required to more completely define the role of SRS monotherapy for patients with RCC brain metastases.

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