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ORIGINAL ARTICLE

Prognostic factors and survival in Japanese patients with brain metastasis from renal cell cancer

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Abstract

Background Patients with brain metastasis from renal cell carcinoma have poor outcomes despite recent advances in diagnosis and treatment. Moreover, factors affecting such poor outcomes are unclear. This study aimed to evaluate the prognostic factors associated with overall survival in renal cell carcinoma patients with brain metastasis.

Methods We retrospectively reviewed the data of 50 consecutive patients with brain metastasis from renal cell carcinoma at our institution between 1988 and 2017. The evaluated prognostic factors for overall survival included clinicopathological factors at diagnosis, treatment for brain metastasis, and the Graded Prognostic Assessment score of renal cell carcinoma. The associations between preoperative clinicopathological factors and overall survival were assessed using the log-rank test and Cox proportional hazards models for univariate and multivariate analyses, respectively.

Results Forty-five patients were included, among whom 39 died during follow-up. The median follow-up was 8.2 months. The median survival time was 8.2 months (95% confidence interval 5.5–13.7). A Graded Prognostic Assessment score ≤ 2 (hazard ratio 1.967; 95% confidence interval 1.024–3.892; $P = 0.042$), the presence of sarcomatoid components (hazard ratio 3.299; 95% confidence interval 1.424–7.193; $P = 0.007$), and no treatment for brain metastasis (hazard ratio 2.594; 95% confidence interval 1.033–5.858; $P = 0.043$) were independently associated with poor prognosis in the multivariate analysis.

Conclusions Patients with renal cell carcinoma who develop brain metastasis have poor overall survival. The Graded Prognostic Assessment score, sarcomatoid components, and treatment for brain metastasis from renal cell carcinoma were independent factors associated with prognosis.

Keywords Brain metastasis · Graded Prognostic Assessment Score · Prognosis · Renal cell carcinoma · Sarcomatoid component

Introduction

Cancers of the kidney and renal pelvis account for approximately 3.8% of all cancers in the United States, with approximately 65,340 new cases diagnosed and 14,970 related deaths in 2018 [1]. The Surveillance, Epidemiology, and End Results registry data show that between 2007 and 2013 approximately 16% of all renal cell carcinoma (RCC) cases were metastatic at diagnosis [2]. The 5-year survival rate of metastatic RCC increased from 7.3% in 1992–1995 to 11.7% in 2007–2013. The median overall survival (OS) of metastatic RCC patients treated between 2004 and 2010 was 18.8 months (95% confidence interval [CI] 17.6–21.4) [3].

Despite these prognostic improvements among RCC patients, those with brain metastasis from RCC still have poor prognosis. Although treatment options for RCC are improving, the median OS for patients with brain metastasis is only 5–10 months [4–6].

Local therapies, including surgery and stereotactic radiosurgery (SRS), can be considered for local control and symptomatic relief and can improve OS. Moreover, supportive

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care remains a mainstay of therapy for RCC patients with brain metastasis [7]. However, only a few prospective studies have assessed treatments for RCC brain metastasis [7–9]. Therefore, no standard treatment modality has been established [8–10].

Prognostic factors are crucial for determining the optimal treatment modality for RCC patients with brain metastasis. Thus, this retrospective study aimed to identify prognostic factors, including the prognostic value of the Graded Prognostic Assessment (GPA) score, in Japanese patients with brain metastasis from RCC.

Methods

Study population

This study was approved by the institutional review board (Approval no.: H29-240) and performed in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. We retrospectively reviewed 50 patients with brain metastasis from RCC at the Chiba Cancer Center between 1988 and 2017. Patients pathologically diagnosed with RCC were included, whereas those lacking pathological data were excluded. Follow-up data were obtained until April 2018.

Study variables

The following data were collected from medical records: sex, age, prior nephrectomy, histology, prior systemic therapy, Karnofsky Performance Status (KPS) score, number of brain metastases, local therapy for brain metastasis, timing of brain metastasis, systemic therapy after brain metastasis diagnosis, date of follow-up, and survival status. All radiographic images of brain metastasis were reviewed by a dedicated neurosurgeon (T.I.). Pathological assessment was performed by experienced pathologists at our institution. Histological subtype was determined according to the 2016 World Health Organization classification. Pathological diagnosis of previous classifications was made by a dedicated pathologist (H.K.). Additionally, we calculated the GPA score for RCC, which is a prognostic index for patients with brain metastasis from various carcinomas [10]. The GPA for RCC comprises KPS and the number of brain metastases and is calculated by adding points for each factor. KPS scores of 70–80 and 90–100 are assigned 1 and 2 points, respectively, whereas 2–3 brain metastases and a single brain metastasis are given 1 and 2 points, respectively. The GPA has a score of 0–4 and OS is significantly longer in patients with high scores.

Systemic therapy before and after brain metastasis, comprising cytokine therapy, targeted therapy (tyrosine kinase inhibitors [TKIs] and mammalian target of rapamycin [mTOR] inhibitors), and immunotherapy, was assessed. Cytokine therapy comprised interferon-alfa and/or interleukin-2. TKI and mTOR inhibitor treatment comprised sunitinib, sorafenib, axitinib, temsirolimus, and everolimus. Nivolumab was used for immunotherapy.

Statistical analysis

The primary endpoint was OS, defined as the period in months from the date of brain metastasis diagnosis via radiographic imaging to the date of either death or last follow-up. The median OS with 95% CI was estimated using Kaplan–Meier analysis. The prognostic significance of each variable was tested in the univariate analysis using the log-rank test. The simultaneous effects of multiple prognostic factors were estimated via multiple regression analysis using the Cox proportional hazards model. Only factors with P values <0.10 were entered into the multiple regression model. The cutoff levels of continuous variables were determined using receiver operating characteristic curve analysis. All statistical analyses were performed using JMP® software, version 12 (SAS Institute Inc., Cary, NC, USA). P values <0.05 were considered significant.

Results

Patient characteristics and treatment

Of the 50 identified RCC patients with brain metastasis, five were excluded owing to missing data. Therefore, 45 patients were included in the analysis. The median follow-up from diagnosis of RCC brain metastasis to death or censorship was 8.2 months. The median OS from brain metastasis was 8.2 months (95% CI 5.5–13.7; Fig. 1). Of the 45 included patients, 39 (87%) died owing to tumor progression during follow-up. Patient characteristics and treatments for brain metastasis are shown in Table 1.

For local treatment, Gamma-Knife radiosurgery was selected for 18 patients whose intracranial lesions were smaller than 30 mm. The peripheral doses of this treatment varied from 18 to 21 Gy, depending on the size of the brain metastasis. No additional irradiation was performed in these patients. Surgical removal for a larger brain tumor was performed in 16 patients. Among these patients, local brain radiation therapy of the surgical cavity with a 20-mm margin at a dose of 60 Gy over 30 fractions was performed immediately after surgery for three patients, whereas whole-brain radiation therapy (WBRT) at a dose of 30–40 Gy over 10–20 fractions was selected for six patients with residual

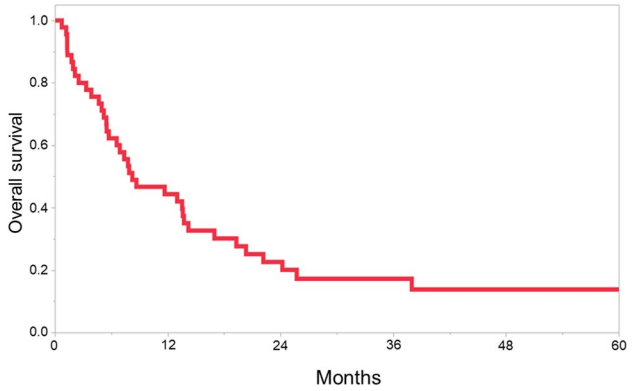

Fig. 1 Kaplan–Meier curve for overall survival in the entire patient cohort

multiple small lesions in the brain parenchyma. No radiation therapy was administered to the remaining seven patients. Three patients with multiple brain metastases were treated by WBRT alone (Table 1).

Eight (18%) patients chose best supportive care. Their median OS was 3.4 months (95% CI 0.7–11.7). The remaining 37 (82%) underwent local therapy for brain metastasis. The median OS among patients receiving local treatments was 13.0 months (95% CI 6.9–17.0; Fig. 2a). Sixteen patients underwent resection of brain metastasis, of whom nine underwent further postoperative radiation therapy.

For the primary lesion, 41 (91%) patients underwent nephrectomy, but only one patient underwent nephrectomy after brain metastasis resection. The median time from initial RCC diagnosis to brain metastasis was 15.6 months (95% CI 8.9–36.6 months). Brain metastasis from RCC was determined during initial diagnosis in 6 (13%) patients. The median OS was 5.6, 6.7, 8.0, 10.8, and 14.2 months for patients with GPA scores of 0, 1, 2, 3, and 4, respectively ($P = 0.153$; data not shown).

Histology was assessed in tissue samples obtained from the kidney ($n = 38$, 84%), brain ($n = 5$, 11%), and bone ($n = 2$, 4%). Thirteen (29%) patients had sarcomatoid components, of whom ten had clear cell RCC. Of the eight patients who underwent no treatment for brain metastasis, four had sarcomatoid components.

After local therapy for brain metastasis, 17 patients started systemic therapy. Among these patients, eight received second-line or higher systemic therapy. As first-line medication, targeted therapy ($n = 9$), cytokine therapy ($n = 6$), and immune therapy ($n = 2$) were administered. Targeted therapy was administered for a median duration of 7.5 months. Sunitinib, temsirolimus, and axitinib were administered to 4, 3, and 2 patients, respectively. Cytokine therapy (interferon-gamma and interferon-alfa) was administered for a median duration of 6.2 months. Nivolumab was administered to 2 patients. The median duration of

Table 1 Patient characteristics ($n = 45$)

Characteristics	Value, *n* (%)
Sex	
Male	28 (62)
Female	17 (38)
Age (years)	
Median (range)	60 (11–82)
Karnofsky Performance Status score	
≥ 90	13 (29)
80	11 (24)
≤ 70	21 (47)
Prior nephrectomy	
Yes	41 (91)
No	4 (9)
Histology	
Clear cell RCC	40 (89)
Chromophobe RCC	1 (2)
Papillary RCC	1 (2)
Mucinous tubular and spindle cell carcinoma	1 (2)
Bellini duct carcinoma	1 (2)
Unclassified	1 (2)
Sarcomatoid components	
Yes	13 (29)
No	32 (71)
Period between RCC diagnosis and brain metastasis (months)	
Median (95% CI)	15.6 (8.9–36.6)
Diagnosis of brain metastasis	
Initial diagnosis of RCC	6 (13)
During follow-up	39 (87)
No. of brain metastases	
1	25 (56)
2–3	9 (20)
≥ 4	11 (24)
GPA score	
≤ 1	12 (27)
2	12 (27)
≥ 3	21 (46)
Extracranial metastasis	
Yes	37 (82)
No	8 (18)
Extracranial metastasis sites	
Lung	30 (67)
Lymph node	11 (24)
Bone	12 (27)
Liver	7 (16)
Other	10 (22)
No. of extracranial metastatic sites	
0	9 (20)
1	13 (29)
≥ 2	23 (51)
No. of prior systemic therapies	
0	19 (42)

Table 1 (continued)

Characteristics	Value, *n* (%)
1	18 (40)
≥ 2	8 (18)
Prior cytokine therapy	
Yes	13 (29)
No	32 (71)
Prior TKI and/or mTOR therapy	
Yes	15 (33)
No	30 (67)
Local therapy for brain metastasis	
None	8 (18)
Stereotactic radiosurgery	18 (40)
Surgery	7 (15)
Surgery + limited brain radiation therapy	3 (7)
Surgery + whole-brain radiation therapy	6 (13)
Whole-brain radiation therapy	3 (7)

CI confidence interval, *RCC* renal cell carcinoma, *GPA* Graded Prognostic Assessment, *TKI* tyrosine kinase inhibitor, *mTOR* mammalian target of rapamycin

first-line treatment was 6.2 months (95% CI 1.6–21.9) and that of second-line treatment was 3.4 months (95% CI 0.9–not reached).

In the patients who underwent brain metastasis treatment, the median OS from diagnosis of brain metastasis in those who did and did not receive succeeding systemic therapy was 13.7 and 7.1 months, respectively ($P = 0.402$). Meanwhile, the median OS of those who received targeted therapy or immunotherapy as first-line therapy was 13.7 months (95% CI 5.0–not reached).

Univariate analysis

All 15 parameters analyzed in the univariate analysis for OS are presented in Table 2. The clinical features associated with poor OS were KPS < 70, ≥ 4 brain metastases, GPA score ≤ 2, no treatment for brain metastasis, non-clear cell histology, and presence of sarcomatoid components on pathology.

Multivariate analysis

The results of the Cox proportional hazards model are shown in Table 2. KPS and the number of brain metastases were excluded because they comprised the GPA score. The independent predictors of poor OS were a GPA score ≤ 2 (hazard ratio [HR] 1.967; 95% CI 1.024–3.892; $P = 0.042$), no treatment for brain metastasis (HR 2.594; 95% CI 1.033–5.858; $P = 0.004$), and presence of sarcomatoid components (HR

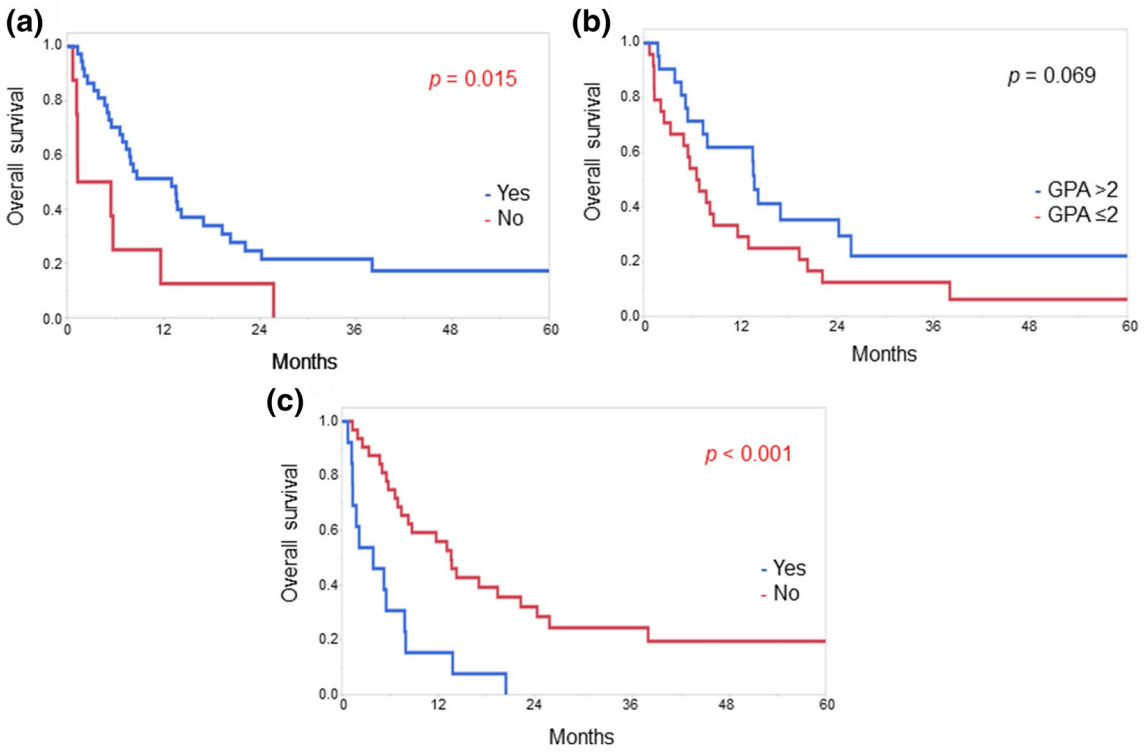

Fig. 2 Kaplan–Meier curve for overall survival stratified by **a** treatment for renal cell carcinoma brain metastasis, **b** Graded Prognostic Assessment, and **c** sarcomatoid components

Table 2 Univariate and multivariate analyses of prognostic factors

Variables	Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	*P* value
Sex	0.346		
Male			
Female			
Age (years)	0.226		
< 65			
≥ 65			
GPA score	0.070		0.042*
> 2		Reference	
≤ 2		1.967 (1.024–3.892)	
Karnofsky performance status score	0.064		
≥ 70			
< 70		–	
No. of brain metastases	0.041*		
< 4			
≥ 4		–	
Prior nephrectomy	0.631		
Yes			
No			
Histology	< 0.001*		0.155
Clear cell RCC		Reference	
Non-clear cell RCC		2.516 (0.690–8.529)	
Sarcomatoid components	< 0.001*		0.007*
No		Reference	
Yes		3.299 (1.424–7.193)	
Period between RCC diagnosis and brain metastasis (months)	0.141		
≥ 12			
< 12			
Timing of brain metastasis diagnosis	0.655		
During initial diagnosis of RCC			
During follow-up			
Extracranial metastasis	0.181		
No			
Yes			
Prior systemic therapies	0.594		
No			
Yes			
Prior cytokine therapy	0.490		
No			
Yes			
Prior TKI and/or mTOR therapy	0.706		
No			
Yes			
Local therapy for brain metastasis	0.015*		0.043*
No		Reference	
Yes		2.594 (1.033–5.858)	

HR hazard ratio, *CI* confidence interval, *RCC* renal cell carcinoma, *GPA* Graded Prognostic Assessment, *TKI* tyrosine kinase inhibitor, *mTOR* mammalian target of rapamycin

*$P < 0.05$

3.299; 95% CI 1.424–7.193; $P = 0.007$). OS plots showed a lower median OS for patients with a GPA ≤ 2 than those with a GPA > 2 (6.7 vs 13.7 months, $P = 0.07$; Fig. 2b). Moreover, OS plots showed a lower median OS for patients with sarcomatoid components than for those without (3.6 vs 13.6 months, $P < 0.001$; Fig. 2c).

Discussion

In this study, we investigated the prognostic factors for RCC patients with brain metastasis to guide optimal treatment. A GPA score of ≤ 2, presence of sarcomatoid components, and no treatment for brain metastasis were the independent factors for poor prognosis.

RCC brain metastasis is associated with poor OS [4], and patients with brain metastasis have poorer survival than those with metastasis to other sites [4, 11]. The median OS in our study was shorter than that reported in other studies because our study population included patients who chose no treatment for brain metastasis [4–7, 12]. However, the OS for patients who received local treatment for brain metastasis in the current study was similar to that previously reported [4–7, 12].

One of the objectives of this study was to find an appropriate treatment for brain metastasis from renal cell cancer. From our results, local treatment was recommended even after brain metastasis, because local brain therapy was an independent prognostic factor in the multivariate analysis. However, we unfortunately could not identify the optimal local treatment for brain metastasis. This study was retrospective, and our patient number was limited. Owing to these limitations, we could not find any significant differences among the local treatment modalities.

In 2008, Sperduto et al. reported that the GPA score was a prognostic index for brain metastasis from various carcinomas. The disease-specific GPA for RCC comprises the KPS score and the number of brain metastases [10, 13]. In the current study, the median OS varied among patients with different GPA scores and ranged from 3.5 to 14.8 months. Similar to previous findings, the GPA score was significantly correlated with OS in our study [10, 13, 14].

Only few studies about the pathological features associated with OS in RCC brain metastasis have been reported [15, 16]. Multivariate analysis showed that, among the histological characteristics, sarcomatoid components were predictive factors of poor prognosis. Sarcomatoid components are a poor prognostic factor for OS in metastatic RCC, and systemic therapies fail to achieve good outcomes in patients with sarcomatoid RCC [17, 18]. Approximately, 6–17% of RCC patients with brain metastasis have sarcomatoid components [15, 16, 19]. Bastos et al. reported that sarcomatoid components were associated with poor OS in RCC patients with brain metastasis who received targeted therapy [16].

Local therapy was associated with better OS than no treatment for brain metastasis. Surgical resection, WBRT, and SRS are the common treatments for brain metastasis. Additionally, the effectiveness of SRS in combination with WBRT has also been examined [20]. However, not all patients are eligible for or agree to local treatment. In these patients, supportive care is an option [9, 21]. The treatment choice for brain metastasis remains uncertain because of the lack of prospective trials on the topic.

The efficacy of targeted therapy for patients with brain metastasis from RCC remains uncertain. Sunitinib is safe for RCC brain metastasis, but the objective response rate is only 12% [22]. Moreover, no prospective data for the efficacy of systemic therapy are available [6, 23]. In our study, the OS of patients who received systemic therapy after brain metastasis was longer than that of those who did not, although the difference was not statistically significant.

This study has some limitations, including its retrospective nature, single-center design, and incomplete data collection. Moreover, this study included patients with heterogeneous features, and no restrictions were made in terms of treatment for brain metastasis, histology, or previous history of treatment with cytokine therapy. These factors should be addressed in future clinical trials.

In conclusion, a GPA score of ≤ 2, presence of sarcomatoid components, and no local treatment for brain metastasis were prognostic factors in RCC patients with brain metastasis. Our results suggest that in the treatment of RCC patients with brain metastasis, local treatment for brain metastasis may improve the prognosis of patients and should be recommended.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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