J Neurooncol (2016) 130:221–228
DOI 10.1007/s11060-016-2238-2

CLINICAL STUDY

Impact of resection and systemic therapy on the survival of patients with brain metastasis of metastatic renal cell carcinoma

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Received: 9 May 2016 / Accepted: 9 August 2016 / Published online: 18 August 2016

Abstract Patients with brain metastasis (BM) from renal cell carcinoma (RCC) are associated with poor prognosis. Between 1990 and 2015, data of consecutive RCC patients with BM were retrospectively analyzed from a urologic oncologic database. The treatment outcome was evaluated by overall survival (OS), which was defined as interval from initial diagnosis of BM to death or last follow-up. Statistical analyses of clinical and pathological variables were performed using Cox regression and the Kaplan–Meier method. A total of 116 RCC patients with BM were included. Median time from initial diagnosis of RCC to BM was 15.8 months (95% CI 11.6–20.0). Median OS after diagnosis of brain metastases of the whole cohort was 5.8 months (95% CI 4.3–7.2). On multivariate Cox regression analysis, age and histology of non-clear cell RCC were associated with poorer outcome, while targeted therapy (n = 26) (OS 9.9 months, 95% CI 3.3–16.5) and BM resection (n = 33) (OS 24.7 months, 95% CI 4–40) were associated with better survival. Furthermore, patients who underwent both targeted therapy and BM resection (n = 5) had the best outcome with median OS of 52.4 months. In conclusion, BM from RCC is associated with a poor oncological outcome. Furthermore, age and histology of non-clear cell RCC are risk factors for poor prognosis. Patients with resectable BM may comprise a better prognostic group. Here, a better OS for resected than unresected patients was observed, which warrants BM resection. A combined modality approach of resection and targeted therapy appears to further improve the outcome of these patients while additional radiation seems to add no benefit.

Keywords Renal cell cancer · Brain metastasis · Targeted therapy · Survival · Prognosis

Introduction

In the past decades, with the improvement of the imaging techniques, patients with renal cell cancer (RCC) are diagnosed at earlier stage and are treated with surgery in curative intention. However, about 30% of patients are still initially diagnosed with metastatic RCC [1] and another 30% of patients with localized disease develop recurrence or metastasis even following curative surgery [2]. The most common site of metastasis from RCC is lung (45–50%), followed by bone (30%) and liver (20%), respectively [3]. Brain metastasis (BM) occurs in approximately 10% of patients with RCC, which is frequently associated with neurological symptoms reducing quality of life [4]. In the literature, BM from RCC is associated with poor prognosis. The natural course of BM from RCC ranges from 3 to 4 months [5]; even a median overall survival (OS) of only 4–11 months

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was observed after diagnosis despite local or systemic treatment [6]. The poor treatment outcome of BM from RCC was attributed to the chemo- and radio-resistant nature of RCC and poor response rates to the historical cytokine therapy along with the poor drug penetration into cerebral metastasis due to the blood–brain barrier.

Local therapy, including surgery and radiation therapy (RT) remains the cornerstone of treatment of BM from RCC [7]. However, the procedure of surgery is challenging, in general requiring an individual therapeutic regimen in selective patients [8]. More recently an evolving understanding of the underlying molecular biology of RCC has dramatically revolutionized the therapeutic scenario of metastatic RCC. The discovery of the VHL mutation in patients with VHL disease, followed by the finding that somatic VHL mutations occur in most sporadic clear cell RCCs, led to the development of agents that target circulating VEGF and VEGF receptors [9]. Since December 2005, several targeted drugs, including sorafenib, sunitinib, pazopanib, bevacizumab and everolimus have been approved for the treatment of advanced RCC both in USA and Europe. The efficacy and safety of these targeted agents have been shown by a series of high-quality randomized controlled trials and bring the treatment of metastatic RCC into the era of targeted therapy [10–17]. However, RCC patients with BM were excluded from the vast majority of prospective studies. Although the safety of sunitinib and sorafenib had been shown in two expanded access trials also enrolling BM patients [18, 19], the efficacy of these agents in BM was only supported by a few small series and case reports trials [20–22]. To date, there is no standard treatment for BM from RCC. The aim of our study was to analyze the survival and prognostic factors in RCC patients with BM following multimodal treatment.

Materials and methods

Study design

After Institutional Review Board approval, data of consecutive RCC patients with BM were extracted from a prospective conducted renal cell cancer database of Heidelberg University Hospital from 1990 to 2015. All patients had given informed consent.

For oncological follow-up in this study, history, physical examination, routine blood workup, and radiographic evaluation according to RECIST were assessed, BM was diagnosed by computed tomography (CT) and/or magnetic resonance imaging (MRI). The demographic, clinical, pathological and laboratory information which were previously found to be of prognostic value were collected. Therapeutic options including surgery for primary and metastatic lesion, chemotherapy, RT, cytokine therapy and targeted therapy were evaluated.

All surgical specimens were processed according to standard pathologic procedures and evaluated by experienced pathologists. Pathologic stage was reassigned according to the 2009 American Joint Committee on Cancer TNM staging system. Tumor histology was classified according to the Heidelberg classification of renal tumors. Tumor cell differentiation was assessed according to Fuhrman nuclear grade.

Statistical analyses

The outcome of this cohort was evaluated with OS, which was defined as time from initial diagnosis of BM to death from any cause or was censored at the date of last follow-up.

The Kolmogorov–Smirnov normality test was used to investigate normal distribution of continuous variables. Univariable and multivariable Cox proportional hazards regression models were performed to evaluate the influence of the clinical and pathologic parameters on mortality of RCC patients with BM. Survival functions were calculated using the Kaplan–Meier method and differences were assessed with the log rank test. All reported p values were two-sided, and statistical significance was set at $p < 0.05$. All tests were done using SPSS®, version 16.0 (Chicago, IL, USA).

Results

Patients and disease characteristics

A total of 116 patients developed BM with a median follow-up period of 32.3 months (95 % CI 20.8–43.9) was identified from 2046 RCC patients between August 1990 and April 2015. As shown in Table 1, histology of clear cell RCC was present in 85.3 % (99/116) of primary tumors. Although 53 of the116 patients (48.3 %) developed distant metastases at initial diagnosis, surgery of primary tumor still was performed in 97.4 % (113/116) of the patients.

The characteristics of 116 patients with BM from RCC were listed in Table 2. At the initial diagnosis of BM, 93.1 % (108/116) of the patients were in favorable performance status (PS) with Karnofsky Performance Status (KPS) ≥70, those eight patients with KPS <70 all belonged to the non-resection group. Median time from initial diagnosis of RCC to BM was 15.8 months (95 % CI 11.6–20.0) and median OS of the whole cohort from diagnosis of BM was 5.8 months (95 % CI 4.3–7.2). Furthermore, the survival rate of 1, 2 and 5 years of this cohort were 30.5, 21.6 and 6.9 %, respectively. In all patients first documented progression was systemic except for two resected patients who had first documented progression

Table 1 Characteristics of primary tumor for 116 RCC patients with brain metastasis

Characteristics	Description
Surgery for primary tumor, n (%)	
Yes	113 (97.4 %)
No	3 (2.6 %)
Laterality of primary tumor, n (%)	
Left	56 (48.3 %)
Right	60 (51.7 %)
Histology, n (%)	
Clear cell	99 (85.3 %)
Non clear cell	6 (5.2 %)
NA	11 (9.5 %)
T stage, n (%)	
1	23 (19.8 %)
2	15 (13.2 %)
3	64 (55.2 %)
4	9 (7.8 %)
NA	5 (4.3 %)
N stage, n (%)	
0	88 (75.9 %)
1	19 (16.4 %)
2	2 (1.7 %)
NA	7 (6.0 %)
M stage, n (%)	
0	46 (36.7 %)
1	53 (45.6 %)
NA	17 (14.7 %)
Fuhrman grade, n (%)	
1	15 (12.9 %)
2	62 (53.4 %)
3	34 (29.4 %)
4	3 (2.6 %)
NA	2 (1.7 %)
Sarcomatoid features, n (%)	
Absent	98 (84.5 %)
Present	7 (6.0 %)
NA	11 (9.5 %)
Local recurrence, n (%)	
Yes	14 (12.1 %)
No	102 (87.9 %)

Table 2 Characteristics of 116 RCC patients with brain metastasis

Characteristics	Description
Clinical features	
Mean age at diagnosis of BM, years (+SD)	62.4 (+10.2)
Gender, n (%)	
Female	33 (28.4 %)
Male	83 (71.6 %)
KPS ≥ 70, n (%)	108 (93.1 %)
Body mass index, n (%)	
≤25.0	45 (38.8 %)
>25.0	59 (50.9 %)
NA	12 (10.3 %)
Sites of initial metastasis	
Brain	42 (36.2 %)
Lung	46 (39.7 %)
Bone	13 (11.2 %)
Other organs	15 (12.9 %)
Number of brain metastases, n (%)	
1	61 (52.6 %)
>1	30 (25.9 %)
NA	25 (21.5 %)
Number of concomitant metastases, n (%)	
0	21 (18.1 %)
1	32 (27.6 %)
2	22 (19.0 %)
>2	41 (35.3 %)
Sites of concomitant metastases	
Lung	80 (69.0 %)
Bone	37 (31.9 %)
Lymph nodes	33 (28.4 %)
Adreanl	14 (12.1 %)
Liver	13 (11.2 %)
Other organs	38 (32.8 %)
Treatment characteristics	
Resection of BM, n (%)	33 (28.4 %)
Radiation therapy, n (%)	74 (63.8 %)
Chemotherapy, n (%)	25 (21.6 %)
Cytokine therapy, n (%)	42 (36.2 %)
Targeted therapy, n (%)	26 (22.4 %)
Given before BM	15 (13.8 %)
Given after BM	11 (7.8 %)

in the brain followed by systemic progression, death was always related to systemic progression and imaging of the brain was mostly not performed during final systemic progression.

In total, 32.6 % (42/116) of the first metastatic lesions were in brain, while 67.4 % (74/114) were in extra-cranial sites including 46 lesions in lungs (39.4 %), 13 lesions in bones (11.5 %) and 15 lesions of other (13.3 %) organs. The median interval between any extra-cranial metastases and BM in this cohort was 5.6 months (95 % CI 3.6–7.6). Among the whole cohort, up to 81.9 % (95/116) of patients had at least one concomitant extra-cranial metastasis, with lung metastasis (n = 80) representing the most common site followed by bone (n = 37) and lymph node (n = 33), respectively. The median OS of patients with vs. without concomitant extracanial metastasis in this cohort were 4.8 vs. 23.4 months ($p = 0.002$). The exact number of BM of 25/116 patients could not be

Table 3 Multivariable COX regression model for prediction of overall survival in 116 RCC patients with brain metastasis

Variable	No.	Median, months (95% CI)	HR (95% CI)	*p* value
Age at BM, years	116	5.9 (4.5–7.4)	1.037 (1.008–1.067)	0.011
Histology				
ccRCC	99	6.3 (4.6–7.8)	0.145 (0.043–0.459)	0.002
Non-ccRCC	6	1.3 (0.3–2.2)		
Sites of initial metastases				
Brain	42	13.3 (9.8–16.8)	0.341 (0.163–0.710)	0.004
Extracranial	74	3.9 (2.8–4.9)		
Targeted therapy				
Yes	26	9.9 (3.3–16.5)	0.446 (0.229–0.871)	0.018
No	90	4.8 (2.7–6.9)		
Resection of BM				
Yes	33	24.7 (9.4–48.0)	0.357 (0.179–0.711)	0.003
No	83	3.7 (2.4–4.9)		

extracted from the files, all those patients had multiple BM and were not resected.

Analyses of prognosis and treatment outcome

On univariate analysis, the impact factors on OS included histology, T stage, N stage, Fuhrman grade, initial metastatic site, pure BM, concomitant metastasis in lung, resection of BM and targeted therapy ($p < 0.05$). All these variables and some other possible impact factors including age, gender, M stage, sarcomatoid features, time from initial diagnosis to BM, time from primary surgery to BM, chemotherapy, RT and cytokine therapy were collected into multivariate analysis.

Clinical and pathological factors for prognosis

On multivariate Cox regression analysis, age, non-ccRCC and initial metastasis at extracranial sites were unfavorable factors for OS of the 116 patients with BM from RCC (Table 3).

In this cohort, the median OS from diagnosis of BM of the patients with initial metastasis in brain (n = 42) vs. extracranial site (n = 74) were 13.3 vs. 3.9 months. OS at 1–2 years were 53.6 vs. 17.4% and 32.2 vs. 15.8% (log rank $p = 0.001$) for brain vs. extracranial metastatic site, respectively. However, the median OS in both groups did not significantly differ from initial detection of any metastatic (13.3 vs. 17.6 months).

Outcome according to classes defined by RTOG PRA analysis

According to suggested Classes by Gapar et al. [23] (Class 1: patients with KPS ≥70, <65 years of age with controlled primary tumor and no extracranial metastases; Class 3: KPS <70; Class 2: all others), for all patients in our cohort the median OS was 7.1 months for Class 1 patients, 4.2 months for Class 2 patients and 2.3 months for Class 3 patients, respectively.

Oncological outcome of multimodal therapy

Local treatment

Only 3 of 116 (2.6%) patients with a median OS of 2.6 months had no surgery for primary tumor in the whole cohort. The remaining 113 (97.4%) patients with a median OS of 5.9 months underwent surgery of primary tumor, including radical nephrectomy (n = 108) and nephron-sparing surgery (n = 5).

Resection of BM was performed in 33 patients, of whom five patients underwent re-resection of BM. Selection for resection was based on presence of solitary metastasis and individual physicians decision. The median age of the patients with BM resection was 63.2 years compared to that of 63.5 years of the patients without BM resection. The patients having extracranial metastases accounted for 63.6% (21/33) in patients with BM resection and 89.1% (74/83) in patients without BM resection, respectively. Except one patient (3.0%) where information is missing, 84.9% (28/33) of resected patients had a solitary BM with a median OS of 27.9 months, while the remaining 12.1% (4/33) of patients had two BMs with a median OS of 7.0 months, respectively. Moreover, 56.0% (65/116) of patients who received whole brain radiotherapy had multiple brain metastases. With respect to surgical margins (SM), R0, R2 and Rx were recorded in 13 (39.3%), 4 (12.1%) and 8 (24.2%) of the 33 patients, respectively. Information on resection status could not be recovered in eight patients (24.2%). As shown in Table 3, whether metastectomy of any other sites being performed or not, the BM resection

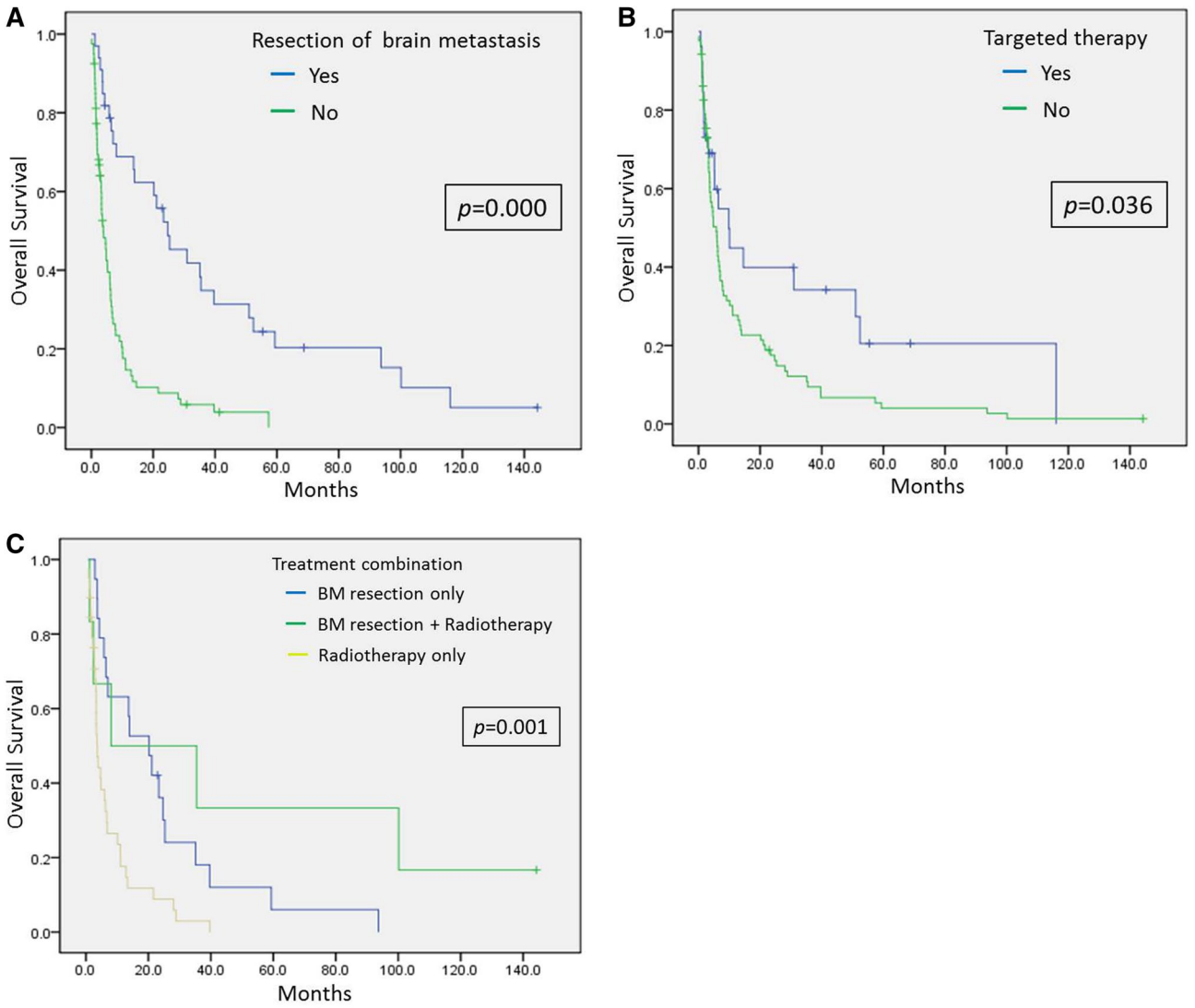

Fig. 1 Overall survival distributions stratified by different treatment or treatment combination estimated by using Kaplan–Meier method and compared by using log rank test. Cohorts of BM resected and unresected patients (**a**). Cohorts of patients receiving target treatment or no targeted treatnment (**b**). Cohorts of radiotherapy to brain, resection of BM or combination of both. Significance for radiotherapy compared to resection is indicated (**c**)

was related to longer OS in the whole cohort. Furthermore, OS rate at 1–2 years were 68.8 vs. 14.1 % and 52.2 vs. 8.4 % for patients with and without resection of BM, respectively ($p = 0.000$, Fig. 1a).

In this cohort, 63.8 % (74/106) of patients underwent RT with a dose ranging from 12 to 42 Gy. The median OS of patients with vs. without RT were 6.3 months (95 % CI 4.4–8.2) vs. 4.8 months (95 % CI 1.5–8.1), whereas no difference was found in between ($p = 0.961$). Among them, stereotactic radiosurgery (SRS) was given to 11 patients with solitary BM and five patients with multiple BMs (2–3 BMs). The median OS of these patients receiving SRS with solitary or multiple BMs were 11.4 and 8.6 months, respectively.

Systemic therapy

Among the 116 patients, median OS of 26 (22.4 %) patients, in which targeted therapy was performed, was significantly higher (9.9 months) compared to patients in whom no targeted therapy was performed (4.8 months, Table 3). Moreover, OS at 1, 2 and 5 years was 44.9 vs. 26.7 %, 39.9 vs. 16.9 % and 20.5 vs. 3.9 % for patients undergoing targeted therapy vs. no targeted therapy, respectively ($p = 0.036$, Fig. 1b).

The median age of patients with targeted therapy was 63.4 vs. 63.2 years without targeted therapy. Moreover, the percentage of patients having extracranial metastases who were treated with targeted therapy or not was 92.3 % (24/26) and 78.9 % (71/90), respectively.

Of the 26 patients receiving targeted agents, 14 patients (53.9%), ten patients (38.4%) and two patients (7.7%) experienced 1, 2 and 3 cycles of targeted therapy, respectively. Up to seven targeted agents including sunitinib, sorafenib, temsirolimus, pazopanib, axitinib evrolimus and imatinib were used in these patients, of whom 46.2% (12/26) received more than one agent sequentially. Sunitinib was dominantly given in 17 patients (65.5%), followed by sorafenib which was given in five patients (19.2%). Furthermore, 61.5% (16/26) of the patients developed BM during the targeted therapy with no difference of OS compared to the remaining ten patients receiving targeted therapy after diagnosis of BM ($p=0.137$). Complete regression (CR), partial regression (PR) and progressive disease (PD) after targeted therapy were observed in one patient (3.8%), four patients (15.4%) and 17 patients (65.4%), respectively. In four patients the oncological behavior could not be determined. Of 25 patients administered chemotherapy, 5-Fluorouracil was dominantly given in 17 patients (68.0%), followed by vinblastine which was given in six patients (24.0%). Meanwhile, a total of 42 patients received cytokine therapy. Among them, 30 patients (71.4%) were given both interferon-α and interleukin-2, while 12 patients (28.6%) were given interferon-α.

However, neither chemotherapy nor cytokine therapy had influence on the survival of the patients in entire cohort ($p=0.604$ and 0.070, respectively).

Multimodal therapy

Only 3 of 116 patients (2.6%) were treated with a combination of BM resection, external beam therapy and targeted agents. OS was 30.0 months, 51.0 months and 116.0 for these three patients, respectively. Meanwhile, the median OS of patients with BM resection *plus* targeted therapy (n=5), BM resection only (n=16) and targeted therapy only (n=5) were 52.4, 8.1 and 3.2 months, respectively. In total, 19 patients underwent surgical resection and adjuvant external beam radiation of brain metastases. Radiation was performed after a median of 45.5 days (range 2–204 days) with a dose ranging from 20 to 40 Gy. As shown in Fig. 1c, the median OS of patients undergoing BM resection + adjuvant RT (n=9), BM resection only (n=16) and RT only (n=39) were 20.2, 8.1 and 3.7 months, respectively ($p=0.001$). Furthermore, the OS of BM resection *plus* RT vs. RT only ($p=0.001$) and BM resection only vs. RT only ($p=0.027$) were significantly different.

Discussion

BM from RCC has been shown to be associated with a poorer prognosis compared to other metastatic lesions in the pre–targeted therapy era [5, 6]. Limited but increasing evidence shows that survival of RCC patients with BM has improved with targeted therapy era [24–26]. The median OS of our cohort was 5.8 months with a survival rate at 1, 2 and 5 years of 30.5, 21.6 and 6.9%, respectively. This is similar to other reports in literature. When comparing patients of our cohort diagnosed before targeted therapy era (before 2006, n=43), OS was similar with an OS of 5.9 months vs. 5.2 for patients treated in the targeted therapy era (n=72, $p=0.364$).We thus tried to identify risk factor and subgroups associated with a poor prognosis.

Although originally developed in 1990, the Motzer model is one of the most commonly used prognostic models for metastatic RCC in the targeted therapy era and proved useful in patients who received sunitinib for metastatic RCC [27]. The Heng score additionally uses neutrophil and platelet count to the four risk factors of the Motzer model (hemoglobin, corrected calcium, ECOG PS and time from diagnosis) as independent prognostic factors for OS in patients receiving targeted agents [28]. However both Motzer model and Heng model lack variables regarding histologic features owing to a relatively low proportion of patients receiving cytoreductive surgery in these series. Considering 97.4% (113/116) of primary tumors were removed in our cohort, we investigated histology as a prognostic factor and found that non-clear cell RCC was associated with shorter OS, which was in line with the result reported by Bastos, D. A. et al. [24]. However, the small sample size has to be considered to interpret these data with caution. The negative impact of age on OS of patients was not beyond expectation. The presence of BM at initial diagnosis was associated with a better OS than occurrence of BM later during the course of the disease, which is to be expected because the survival at a later stage of the disease is shorter than at initial diagnosis. In accordance, OS from initial metastasis at any site showed no difference between the groups with initial metastasis in the brain or at an extracranial site (13.3 vs. 17.6 months, $p=0.214$).

In this study, resection of BM significantly increased OS from diagnosis of BM. Although radiotherapy alone showed no positive effect on survival, combination of BM resection and postoperative radiotherapy further improved the OS of patients with BM from RCC. Of note, at initial diagnosis BM was resected in 54.5% (18/33) of patients compared to 45.5% (15/33) of patients during the course of disease which is quite comparable. Remon, J. et al. stated the outcome in patients undergoing aggressive local treatment of brain metastases was greatly influenced by patient selection, BM resection with postoperative radiotherapy or SRS for patients with a limited number of brain metastases should be the standard of care, particularly in patients with good PS and with controlled extracranial disease despite no consensus [8]. This is in accordance with our cohort of patients receiving BM resection or SRS who mostly had favorable PS and solitary cranial lesion.

The advent of targeted agents has dramatically altered the management of metastatic RCC. However, the efficacy of targeted therapy for patients with BM from RCC remains controversial due to lack of high quality evidence from randomized clinical trial. In a cohort of 338 patients, sunitinib or sorafenib both provided a significant survival benefit and might reduce the incidence of BM [22].The mechanism might be contributed a better crossing of targeted agents through the blood–brain barrier than previously used cytokines [29] The present study confirmed this and further revealed targeted therapy combined with BM resection might have the best impact on prognosis. However, this conclusion should be drawn with caution considering selection bias and low patient´s number. Further studies with a large patient cohort using targeted therapy in the treatment of BM are warranted.In 1997, Gaspar, et al. developed a three-class prognostic system analyzing 1200 patients from three consecutive Radiation Therapy Oncology Group (RTOG) trials conducted between 1979 and 1993 [23]. Although the majority of publications regarding RTOG PRA classification were reviewed in patients with BM from lung cancer, a median OS of RCC patients with BM was reported as 8.5 months for Class 1 (n = 2), 3.0 months for Class 2 (n = 37) and 0.6 months for Class 3 (n = 7), respectively ($p = 0.0834$) [30].

In our cohort we could validate the prognosis difference, albeit with longer survival of all Classes compared to those published highlighting the medical progress.

In general, patients that qualify for resection because of solitary lesions in the brain may represent a favorable prognosis group irrespective of treatment. The oncologic outcome for the BM resection cohort is similar to those of patients without BM. Thus, we think resection is warranted for this patient cohort and combination with targeted treatment appears to further improve the prognosis.

The limitations of the current study are based on the inherent nature of one-arm and retrospective study design. Additionally, some details of the pretreatment characteristics and therapeutic information were unavailable because the data collection of the original database was not specially designed to examine BM. Also selection for resection for solitary metastasis was not uniformely stratified but often based on individual physicions preference. In the future, well-designed prospective clinical trial concerning BM from RCC with RTOG PRA classification will be considered.

Conclusion

BM from RCC is related to a poor oncological outcome. Furthermore, age and histology of non-clear cell predict a worse prognosis. Optimal management of BM from RCC should be generally conducted on an individual basis. Targeted therapy and resection of BM in selected patients might improve the survival of RCC patients with BM, particularly the combination of both might achieve this effect to the best advantage.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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