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Improved Survival Outcomes for Kidney Cancer Patients with Brain Metastases

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Abstract

Background: Brain metastases (BM) occur frequently in patients with metastatic kidney cancer and are a significant source of morbidity and mortality. While historically associated with a poor prognosis, survival outcomes for patients in the modern era are incompletely characterized. In particular, outcomes after adjusting for systemic therapy administration and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk factors are not well known.

Methods: A retrospective database of metastatic RCC patients treated at UT Southwestern Medical Center between 2006 and 2015 was created. Data relevant to their diagnosis, treatment course and outcomes was systematically collected. Survival was analyzed by the Kaplan-Meier method. BM patients were compared to non-BM patients after adjusting for the timing of BM diagnosis, either prior to or after first-line systemic therapy. The impact of stratification according to IMDC risk group was assessed.

Results: 56 of 268 patients (28.4%) with metastatic RCC were diagnosed with brain metastases (BM) prior to or during first-line systemic therapy. Median OS for systemic therapy-naïve BM

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patients compared with matched non-BM patients was 19.5 vs. 28.7 months ($p=0.0117$). When analyzed according to IMDC risk group, median OS for patients with BM was similar for favorable and intermediate-risk patients (NR vs NR; and 29.0 vs. 36.7 months, $p=0.5254$), and inferior for poor-risk patients (3.5 vs 9.4 months, $p=0.0462$). For patients developing BM while on first-line systemic therapy, survival from the time of progression did not significantly differ by presence or absence of BM (11.8 vs. 17.8 months, $p=0.6658$).

Conclusions: Survival rates for patients with BM are significantly better than historical reports. After adjusting for systemic therapy, survival rates of patients with BM in good and intermediate-risk groups were remarkably better than expected and not statistically different from patients without BM, though this represents a single institution experience and numbers are modest.

Micro-abstract: In this study, we analyze survival for metastatic renal cell carcinoma patients with brain metastases compared with disease-matched patients without brain metastases, adjusting for line of systemic therapy and IMDC risk group. We observed that the development of brain metastases did not significant impact survival for favorable and intermediate-risk patients, while poor-risk patients with brain metastases fared worse.

Keywords

Renal cell carcinoma; brain metastases; stereotactic radiosurgery

Background:

Brain metastases (BM) are a significant source of morbidity and mortality in patients with metastatic renal cell carcinoma (RCC). The incidence of BM in patients with metastatic RCC varies between series but generally falls between 5 and 15%.¹⁻⁴ The reported median overall survival from diagnosis of BM also varies widely from just a few months in older series to around one year most recently.⁵⁻⁸

Targeted therapies, including vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF-TKIs), mammalian target of rapamycin complex 1 (mTORC1) inhibitors, and immune checkpoint inhibitors including anti-programmed death receptor 1 (PD-1) and anti-cytotoxic T-lymphocyte associated protein-4 (CTLA-4) monoclonal antibodies, have resulted in steady improvements in overall survival for patients with extracranial metastatic RCC. There is conflicting evidence as to whether these agents are effective in treating BM.⁸⁻¹¹

In the past, whole brain radiotherapy (WBRT) was frequently used in patients with BM. RCC is relatively resistant to radiation delivered in conventional fractionated doses as are used for WBRT.¹² As a consequence, intracranial progression was frequent and survival was often short.¹³ Local control rates are better in appropriately selected patients treated with neurosurgical resection (NS) or stereotactic radiosurgery (SRS), however most patients either go on to develop new sites of intracranial disease, or succumb to progression of extracranial disease.¹⁴ Unfortunately, patients with BM are frequently excluded from prospective clinical trials, making outcomes from BM in the currently era of multiple targeted therapies difficult to assess. In this study we seek to analyze the outcomes for

metastatic RCC patients with BM treated with modern systemic and local therapies compared to disease-matched non-BM patients.

Methods:

Study Design

Following approval by the Institutional Review Board, a database of patients with metastatic RCC treated between January 2006 and October 2015 was retrospectively compiled. Patients were identified by the International Classification of Diseases, Ninth Revision diagnostic code for RCC and their medical records reviewed. All identified patients with metastatic RCC treated and followed by medical oncologists at the University of Texas Southwestern Medical Center between January 2006 and October 2015 were included. Follow-up extended until November 2016. Systemic therapy was defined as either a VEGF-TKI, the anti-VEGF monoclonal antibody (mAb) bevacizumab, mTORC1 inhibitors or immunotherapy (interleukin-2, interferon or the anti-PD-1 mAb nivolumab). Patients that received only brain metastasis-targeted local treatment (WBRT, SRS, or NSR) and received no systemic treatment or follow-up with medical oncology at our institution were excluded from the analysis in an effort to minimize referral bias. Generally, the practice at our institution is to screen for BM during the initial work-up for all metastatic RCC patients and periodically thereafter, often when there is progression and a change in systemic therapy, or as clinically indicated. This is typically done with magnetic resonance imaging (MRI). The diagnosis of BM was made based on characteristic radiographic findings, except where pathologic confirmation following surgical resection was available. Patients were assigned to a risk group according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model.⁹ Patients with BM diagnosed during their initial metastatic work-up are compared with patients similarly diagnosed with metastatic disease, but without BM. Since the development of BM represents a progression event, BM patients are compared to matched non-BM patients at the same phase of their disease. For example, patients who progressed to develop BM during first-line systemic therapy are compared with non-BM patients at the time of progression on first-line systemic therapy.

Patient Selection

Because the Kidney Cancer Program at UT Southwestern has a significant regional and national referral base, we sought to mitigate this influence on our metastatic RCC and RCC BM cohorts. A total of 331 patients with metastatic kidney cancer were identified as receiving treatment at our institution during this search. 36 patients were referred for interventional specialty care only (most commonly radiation oncology or surgery), including 6 patients with brain metastases. 27 patients were seen in a medical oncology clinic only once, the majority for the stated goal of a second opinion. The remaining 268 patients had a longitudinal relationship with our institution and their data were collected for this analysis.

Data Collection

Demographic, clinical, pathologic, radiographic, and laboratory data relevant to the patients' diagnosis, treatment, and outcomes were extracted by physician review of the electronic medical record. Beginning and end dates for all lines of systemic therapy as well as baseline

laboratory values and Karnofsky performance status at the start of each line of medical therapy and at the time BM diagnosis were collected.

Statistical Analysis

Survival outcomes were defined as time from the event of interest (eg. diagnosis of BM, diagnosis of metastatic RCC, or progression) to death from any cause, with surviving patients censored at the time of the most recent follow-up. BM patients were divided by line of medical treatment into two cohorts: systemic treatment-naïve and those progressing after receiving first-line systemic therapy. These two BM cohorts were compared against non-BM metastatic RCC patients matched to the same phase of their treatment. Patient characteristics of the BM and non-BM cohorts were compared using the Wilcoxon Rank-Sum test for continuous measures and the Chi-Square test for categorical measures. Overall survival was calculated by the Kaplan-Meier method with differences assessed by the log-rank test. Univariate and multivariate Cox regression analysis were used to analyze risk factors for death. All statistical analyses were performed at the 0.05 significance level using SAS 9.4 (SAS Institute Inc., Cary NC).

Results:

Patients

268 patients with metastatic renal cell carcinoma were identified, of whom 76 (28.4%) were diagnosed with BM. 20 patients were diagnosed with BM after multiple lines of therapy (second-line 8, third-line 4, fourth-line 5, and fifth-line 3). These patients were not included in the analysis as the small numbers on each line of therapy would not allow for meaningful comparison with a matched cohort of non-BM patients. Inclusion or exclusion of these patients did not significantly change the median overall survival from the diagnosis of metastatic RCC among BM patients (both 26.4 months). Of the remaining 248 patients, 56 were diagnosed with BM prior to or during first-line therapy. Patient characteristics are presented in Table 1. Patients with BM were more likely to have clear cell RCC (93.8 vs. 81.0%, $p=0.0344$) and had a higher T-stage at diagnosis. Details of first-line systemic therapy are reported in the supplement (Table S1). The remaining characteristics were not significantly different between the two cohorts, including age, race, sex, Fuhrman grade, or IMDC risk group.

Among BM patients, 35 (62.5%) were diagnosed prior to starting systemic therapy (therapy-naïve). The majority (31/35) were diagnosed with BM during the initial evaluation for metastatic disease. 4 patients with indolent disease were being observed without systemic therapy at the time of BM diagnosis. Details of the timing of metastatic and BM diagnoses are reported in Table S2 of the Supplement. The remaining 21 BM patients (37.5%) were diagnosed after starting first-line systemic therapy. This occurred after a median of 17.3 months from metastatic diagnosis. This included 6 patients who had received high-dose IL-2 as first-line therapy and subsequently enjoyed an extended progression-free interval.

Systemic Therapy-naïve

The median OS for systemic therapy-naïve patients with BM was inferior to that of non-BM (19.5 vs. 28.7 months, $p=0.0117$, Figure 1A). Median OS for favorable-risk systemic therapy-naïve patients (Figure 2A) was not reached for both BM and non-BM patients (Table 2). For intermediate-risk, median overall survival was 29.0 months for those with BM, compared with 36.7 months for those without, which was not significantly different ($p=0.5254$, Figure 2B). This difference remained not significant ($p=0.1147$) when favorable and intermediate-risk patients were analyzed together (Supplement, Figure S2A). Poor-risk patients with BM did significantly worse than those without (3.5 vs 9.4 months, $p=0.0462$, Figure 2C).

Progression on First-line Systemic Therapy

Of 21 patients diagnosed with BM during first-line systemic therapy, 18 (85.7%) had a negative baseline MRI done for staging purposes a median of 6.7 months (range 2.2 – 24.2 months) prior to BM diagnosis. First-line therapy consisted of an anti-VEGF agent (TKI or mAb) for 51.7% ($n=12$), immunotherapy (predominantly high-dose IL-2) for 28.6% ($n=6$), and an mTORC1 inhibitor in 14.4% ($n=3$). Details are included in the supplement, Table S1.

In this cohort, BM were diagnosed after a median of 9.0 months on systemic therapy. From the time of progression on first-line therapy, median OS was 11.8 months compared with 17.8 months for non-BM patients. While numbers are small, this was not significantly different ($p=0.6658$, Figure 1B). This held true when stratified by IMDC risk group for favorable and intermediate-risk (NR vs 56.9 months, $p=0.258$; and 10.9 vs 22.3 months, $p=0.308$, respectively. See Supplement, Figure 2A-B). This difference remained not significant ($p=0.2362$) when favorable and intermediate-risk patients were analyzed together (Supplement, Figure S2B). Poor-risk patients with BM again did worse than patients without BM (mOS 1.1 vs 5.0 months, $p=0.055$), although there were few patients in each group (Supplement, Figure S1C).

Survival from Metastatic RCC Diagnosis

Survival from the diagnosis of metastatic disease was analyzed among all patients, stratified by whether they were diagnosed with BM at any point (prior to or during first line therapy). All risk groups were included. Median OS from the diagnosis of metastatic RCC for patients diagnosed with brain metastases at any point was 26.4 months, compared with 28.7 months for patients never diagnosed with brain metastases ($p=0.4517$, Figure 3).

CNS-directed Therapy

52 of 56 patients (92.9%) received a CNS-directed treatment for BM. 9 patients were treated with WBRT, 21 with SRS, and 8 with NS, all as monotherapy at diagnosis of their BM. 14 patients were treated with more than one modality at various times in their course (5 WBRT + SRS, 6 SRS + NS, 1 WBRT + NS + SRS). In total, 43 patients (77% of those receiving treatment) received a BM-only therapy (NS or SRS) without prophylactic coverage of the entire brain. 4 patients received no BM therapy. Of these, 1 patient went on hospice immediately following BM diagnosis, 1 planned to receive SRS but expired before treatment, 1 had a small solitary BM which became unappreciable after changing therapy

from pazopanib to everolimus, and 1 patient was lost to follow-up. For further details regarding local treatments, see accompanying publication by Wardak and colleagues.

Univariate and Multivariate Analysis of Survival

For patients who had not yet started systemic therapy, the development of brain metastasis and the IMDC risk group were independent risk factors for death in both univariate and multivariate analysis (Table 3). However, among patients progressing after first-line therapy, brain metastases were not independently associated with an increased risk of death in either univariate (HR 1.14, 95% CI 0.64 – 2.02) or multivariate (HR 1.92, 95% CI 0.99 – 3.73) analysis.

Discussion:

In this retrospective study, we report overall survival outcomes of RCC patients diagnosed with BM prior to or during first-line systemic therapy compared with RCC patients without BM similarly treated within the same institution. We observed that overall survival after BM diagnosis was 19.5 months for therapy-naïve and 11.8 months for first-line therapy patients. This was significantly better than what has been historically reported, which is typically less than 12 months for all BM patients.^{7,8} IMDC risk group continued to have prognostic significance following the diagnosis of BM, with survival for favorable and intermediate-risk patients not significantly different from patients without BM. Only poor-risk patients with BM fared significantly worse. We also observed that IMDC risk group carried greater prognostic significance than the presence of BM.

Outcomes for metastatic RCC patients with BM would intuitively be expected to improve with advances in local and systemic therapy. While the diagnosis of RCC BM has been historically associated with a poor prognosis, all of the patients reported here received modern systemic therapies and had access to specialists proficient in local treatment of RCC BM, including surgical resection and SRS.^{3,5,15} Indeed, WBRT was used in only a small subset of patients and the frequency of use decreased over time. Currently, at our institution, WBRT is rarely used.

Without accounting for the timing of BM development, even patients treated with modern systemic and local therapies have reported median OS from BM diagnosis of only approximately 12 months.⁷ In recent studies, this figure typically includes both newly diagnosed metastatic RCC patients and those at all subsequent stages of their disease. But the expected survival in these circumstances is necessarily very different. Disregarding the timeline of BM development within the disease's natural history fails to fully appreciate the impact of tumor burden and lines of therapy on survival. While perhaps less of an issue in the past, fortunately now patients often receive multiple lines of systemic therapy which are able to effectively alter the natural history of the disease. Comparing BM patients with a cohort of similarly treated non-BM patients contextualizes the development of BM within the overall disease trajectory in a way that has not been previously reported to our knowledge.

Systemic therapy-naïve BM patients had a median OS of 19.5 months compared with 28.5 months ($p=0.0117$) for those without BM. This inferior survival in BM patients is driven by a sharp 25% drop in survival within the first 6 months following the diagnosis, with most deaths occurring in the poor-risk group (9 of 11 deaths). After this initial high-mortality period, survival curves between the two groups are quite similar (Figure 1A). There was no increase in early mortality among BM patients diagnosed after first-line systemic therapy.

The OS for patients who developed BM after first-line systemic therapy did not differ significantly from patients without BM (11.8 vs. 17.8 months, $p=0.6658$). Furthermore, BM were not associated with an increased risk of death in this group in either univariate or multivariate analysis. It is possible that with a larger sample size this would have reached significance, particularly in the multivariate. These findings suggest that the prognosis at time of progression on first-line therapy is similar regardless of whether progression is intracranial or extracranial. Unlike the systemic therapy-naïve group, here there was no increased early mortality among BM patients. This may in part be due to a higher early death rate among non-BM who progressed on first-line systemic therapy. There were also fewer BM patients with poor-risk disease in this group compared with the systemic therapy-naïve cohort (14.3% vs. 34.3%). Poor-risk RCC occurred at similar rates among the non-BM patients in the systemic therapy-naïve and first-line therapy groups (21.9 vs. 22.3%).

Several factors may be contributing to better than expected survival in BM patients. First, MRI is increasingly used for screening of BM at diagnosis. Multiple guidelines recommend CNS imaging during the work-up for metastatic RCC only when it is clinically indicated.^{16,17} Our institutional practice is to obtain CNS imaging, preferably with MRI and using gadolinium, in all newly diagnosed metastatic patients. This may have increased the number of patients diagnosed early with asymptomatic disease. A recent trial of active surveillance for metastatic RCC observed several cases of symptomatic CNS progression and as a result routine CNS imaging was recommended and incorporated into the protocol.¹⁸ While repeated brain MRI imaging is frequently often performed at progression (or when symptoms arise), the early detection and treatment of BM, particularly in patients with otherwise stable extracranial disease, may have contributed to improved outcomes for our patients.

Second, 77% of BM patients received a directed local therapy (SRS and/or NS). In older series, WBRT was the primarily modality of CNS-directed treatment, and resulted in short-lived local control.¹³ CNS-directed therapies such as SRS are generally quite effective at providing more durable local control of BM, and when intracranial progression occurs, it is usually at new sites within the brain and is associated with progression of extracranial disease as well.¹⁹ It is the practice at our institution to continue the current systemic therapy when extracranial sites of disease continue to respond if BM are not extensive and can be effectively treated (with SRS or NS).

These data also suggest that control of extracranial disease is an important determinant of survival for patients with BM. The most significant evidence for this observation is that CNS control in our experience is very high (see accompanying publication by Wardak and colleagues). Further supporting this argument is the fact that risk group continues to have

prognostic value for survival following a BM diagnosis. Poor-risk BM patients generally do poorly in both the systemic therapy-naïve and first-line treated setting, whereas survival for favorable and intermediate-risk patients is comparable to patients without BM (Supplement, Figure S1 and S2). While our data does not reveal whether brain or extracranial metastases were the primary contributor to mortality in the poor-risk group, poor-risk patients are less likely to respond to salvage systemic therapy.^{20, 21} Furthermore, poor-risk patients are overrepresented among the early deaths in the systemic therapy-naïve BM patients, and it seems likely these patients had primary refractory extracranial disease as well. Most patients were treated first-line with a VEGF-TKI, so what effect the introduction of anti-CTLA4 and anti-PD1 combination immunotherapy, particularly efficacious in intermediate and poor-risk patients, might have on outcomes remains to be seen.^{22,23}

The impact of systemic therapies on intracranial disease also remains uncertain. As most clinical trials exclude patients with untreated BM, prospective data is lacking. Small series and case reports document intracerebral responses to VEGF-TKI, and animal models show sunitinib achieves meaningful concentrations in the cerebrospinal fluid.^{24,25} In the prospective TARGET trial, sorafenib appeared to decrease the incidence of CNS metastases compared with placebo.²⁶ Similarly, immune checkpoint inhibitors have shown promise in treating melanoma BM, alone and in combination with SRS.^{27–30} Only 6 BM patients in our series had received immune checkpoint inhibitors by the end of follow-up, which suggests that the improvements observed in BM patients is unlikely to be driven by them.

In a series by Du and colleagues, survival from the initial diagnosis of metastatic RCC was not impacted by a diagnosis of BM at any point during their treatment.³¹ This was also the case for our patients (Figure 3). This is particularly significant in our population where 65% of patients were diagnosed with BM prior to starting any systemic therapy. This further reinforces the idea that BM need not grievously impact survival if they can be treated with effective local therapies. Only patients with poor-risk RCC who developed BM fared worse, regardless of when BM were diagnosed, suggesting that risk group should be considered when counseling patients regarding prognosis and treatment strategies for BM. It is also worth noting that outcomes are not universally poor, and among the 12 patients with poor-risk disease presenting with BM, two patients were alive 1.5 years or beyond. The increasing use of immune checkpoint inhibitors may further improve outcomes in poor-risk patients.^{22,23}

Finally, the incidence of BM in our patient population (28.4%) is higher than in most prior studies. Historically the incidence of BM in metastatic RCC patients has been cited around 10% in several clinical series, and up to 15% at autopsy.³² One possible explanation for this increase over historical rates is that BM are being more frequently diagnosed due to improved imaging techniques and the wider adoption of MRI with contrast for both screening and diagnosis of BM. Furthermore, as overall survival with metastatic RCC improves thanks to more effective therapies, more patients may be surviving to develop BM as a subsequent site of progression. This phenomena has been observed in other tumor types.³³

Limitations:

Our study has several limitations. The study is retrospective in nature and BM were diagnosed clinically by the treating oncologists based on radiographic findings. Furthermore, CNS imaging was not performed according to a pre-established protocol and was retrospectively reviewed, raising the possibility that undiagnosed cases of BM could be present in the non-BM group. These data also represent the experience of a single academic center that includes a referral population for BM treatment. As noted under Methods we have attempted to minimize this particular referral bias by limiting the study population to patients treated by medical oncologists at our institution, thus excluding patients who may have been referred solely for local treatment of BM.

Conclusion:

The development of brain metastases did not significantly influence survival for patients with favorable and intermediate-risk RCC when diagnosed prior to or during first-line systemic therapy. Excessive BM-associated mortality occurred in poor-risk patients, suggesting that IMDC risk group and control of extracranial disease should be carefully weighed when considering treatment options and prognosis for RCC patients that develop BM. Our data suggests that aggressive local therapy approaches aimed at durable local control of BM are effective and appropriate in favorable and intermediate-risk patients. Poor-risk patients need better therapies and may particularly benefit from dual checkpoint inhibitors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points:

- Patients with RCC brain metastases and good or intermediate-risk disease achieved similar survival to patients without brain metastases when treated with modern systemic and local therapies.
- Brain metastases were associated with shorter survival in patients with poor-risk RCC.
- IMDC risk stratification remains prognostic in RCC patients with brain metastases.

Figure 1.

Overall survival of all patients stratified by presence of brain metastasis (BM). A, Survival for patients with BM diagnosed prior to starting systemic therapy compared with survival from metastatic RCC diagnosis in patients who did not develop BM. B, Survival from diagnosis of BM after start of first-line of systemic therapy compared to patients without BM at the time of progression on 1st line systemic therapy.

Figure 2.
Overall survival from diagnosis of metastatic RCC by presence of brain metastasis in patients without prior systemic therapy (see Fig. 1A) according to IMDC risk group.

Figure 3:
Overall survival from the diagnosis of metastatic RCC in patients diagnosed with BM prior to or during 1st-line systemic therapy (26.4 months; 95% CI: 14.3–39.6) compared with patients never diagnosed with BM (28.7 months; 95% CI: 22.0–39.7).

Table 1.**Patient Characteristics**

	BM present (n = 56)	BM absent (n = 192)	p
Median age at met dx (range)	61.1 (28.4–76.1)	61.9 (24.5–85.1)	0.1147
Gender			0.1592
Female	19 (33.9%)	47 (24.5%)	
Male	37 (66.1%)	145 (75.5%)	
Race			0.8638
Non-white	20 (36.4%)	66 (35.1%)	
White	35 (63.6%)	122 (64.9%)	
Unavailable	1	4	
Prior nephrectomy			0.6655
No	15 (26.8%)	46 (24.0%)	
Yes	41 (73.2%)	146 (76.0%)	
Histology			0.0344
Non-ccRCC	3 (6.3%)	33 (19.0%)	
ccRCC	45 (93.8%)	141 (81.0%)	
Unavailable	8	18	
Grade			0.8851
1	2 (4.9%)	4 (2.7%)	
2	9 (22.0%)	30 (20.4%)	
3	20 (48.8%)	72 (49.0%)	
4	10 (24.4%)	41 (27.9%)	
Unavailable	15	45	
pT			0.0459
1	3 (6.3%)	40 (23.1%)	
2	7 (14.6%)	30 (17.3%)	
3	33 (68.8%)	91 (52.6%)	
4	5 (10.4%)	12 (6.9%)	
Unavailable	8	19	
pN			0.5083
X	19 (33.9%)	51 (26.6%)	
0	22 (39.3%)	78 (40.6%)	
1	15 (26.8%)	63 (32.8%)	
M [†]			0.2565
0	19 (38.0%)	45 (29.4%)	
1	31 (62.0%)	108 (70.6%)	
Unavailable	6	39	
KPS at mets dx			0.2735
0–70	13 (30.2%)	36 (22.2%)	
80–100	30 (69.8%)	126 (77.8%)	
Unavailable	13	30	

	BM present (n = 56)	BM absent (n = 192)	<i>p</i>
Risk group			0.8753
Favorable (0)	10 (19.6%)	28 (17.9%)	
Intermediate (1–2)	26 (51.0%)	86 (55.1%)	
Poor (3–6)	15 (29.4%)	42 (26.9%)	
Unavailable	5	36	

[†]TNM staging refers to staging at the time of the initial pathologic diagnosis of RCC. All patients had M1 disease at the start of this study.

Table 2.

Median OS (in months, 95% CI) by presence of BM and prior therapy

	BM present	BM absent	<i>p</i>
No prior therapy (n = 35/192)	19.5 (6.3–29.0)	28.7 (22.0–39.7)	0.0117
Favorable risk (n = 4/28)	Not reached	Not reached	0.0240
Intermediate risk (n = 18/86)	29.0 (11.4–58.7)	36.7 (19.4–44.4)	0.5254
Poor risk (n = 12/42)	3.5 (2.6–6.3)	9.4 (4.6–13.6)	0.0462
1 prior therapy (n = 21/166)	11.8 (2.9–87.3)	17.8 (11.7–24.4)	0.6658
Favorable risk (n = 6/25)	Not reached	56.9 (26.6–*)	0.2578
Intermediate risk (n = 8/74)	10.9 (1.5–87.3)	22.3 (10.6–35.5)	0.3079
Poor risk (n = 3/37)	1.1 (0.1–*)	5.0 (2.4–8.5)	0.0550

Table 3.

Survival analysis

	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	<i>p</i>	Hazard Ratio (95% CI)	<i>p</i>
No prior therapy				
Brain metastases				
Absent	Reference	0.0128	Reference	0.0304
Present	1.72 (1.12, 2.63)		1.65 (1.05, 2.59)	
Risk group				
Favorable (0)	Reference	<0.0001	Reference	<0.0001
Intermediate (1–2)	2.91 (1.49, 5.68)		2.78 (1.42, 5.43)	
Poor (3–6)	10.37 (5.17, 20.81)		10.25 (5.11, 20.58)	
Age (per year increase)	0.99 (0.97, 1.01)	0.1779	1.00 (0.98, 1.02)	0.7832
One prior therapy				
Brain metastases				
Absent	Reference	0.6661	Reference	0.0538
Present	1.14 (0.64, 2.02)		1.92 (0.99, 3.73)	
Risk group				
Favorable (0)	Reference	<0.0001	Reference	<0.0001
Intermediate (1–2)	2.03 (1.03, 4.00)		2.11 (1.07, 4.17)	
Poor (3–6)	5.73 (2.82, 11.64)		6.51 (3.16, 13.43)	
Age (per year increase)	1.00 (0.98, 1.01)	0.5904	1.01 (0.99, 1.03)	0.4382