Brain and leptomeningeal metastases from cutaneous melanoma: Survival outcomes based on clinical features

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Brain metastases (BM) are among the most devastating and debilitating complications of melanoma. This retrospective study was conducted to gain a better understanding of patient and disease characteristics that have the greatest impact on overall survival in melanoma patients with BM; therapeutic interventions were also assessed. The records of all patients diagnosed with cutaneous melanoma and BM who were seen at Memorial Sloan-Kettering Cancer Center between 1991 and 2001 were retrospectively reviewed. A variety of factors, including age at diagnosis of stage IV disease, gender, race, disease stage at diagnosis, presence of BM at diagnosis of stage IV disease, neurologic symptoms, radiographic findings, number of BM, status and site(s) of extracranial metastasis, and treatment modalities, were analyzed for correlation with overall survival using univariate and multivariate Cox regression models. The records of 355 patients with BM were included in the analysis. On univariate analysis, seven patient and disease characteristics were significantly associated with poorer survival: age > 65 years, extracranial metastases, BM at stage IV diagnosis, neurologic symptoms, four or more BM, hydrocephalus, and leptomeningeal metastases. Of these, age, extracranial metastasis, neurologic symptoms, and number of BM were significantly associated with poorer survival in a multivariate analysis. Multivariate analysis of treatment modalities suggested that patients who had surgery, radiosurgery, or chemotherapy with temozolomide had improved survival outcomes, although this analysis has limitations. The prognostic factors identified in this retrospective study should be considered when making treatment decisions for patients with BM and used as stratification factors in future clinical trials.
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Melanoma is the third most common tumor to metastasize to the brain. The reported incidence of brain metastases (BM) is 10% to 40%, but many patients may have subclinical BM, as evidenced by a higher reported incidence at autopsy (12%–73%) and the frequent discovery of asymp-

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tomatic BM on brain imaging studies.[1–3] The median survival for patients with untreated BM is only weeks. With treatment, most patients will live less than 1 year from diagnosis of BM, but a few long-term survivors have been reported.[1,3,4–12] Historically, the majority of patients with melanoma BM die a neurologic death, although the incidence varies depending on the extent of extracranial metastases.[1–3,8,9,12–17] The reason for this dismal outcome is the relative resistance of melanoma to radiation and chemotherapy. Treatment approaches for patients with BM include surgery, whole-brain radiotherapy (WBRT), radiosurgery (RS), and systemic chemotherapy, although systemic chemotherapy has historically had a limited impact on survival. The selection of treatment modality or combined modalities is often based on factors unique to each individual patient and his or her disease. In general, the goal of therapy is to stabilize intracranial disease and improve quality of life.

To better understand the prognostic factors that influence survival in patients with melanoma and BM, we conducted a retrospective analysis of patient- and disease-related factors. Many of these prognostic factors have not been evaluated previously, and their impact on survival is unclear. A better understanding of these factors may allow for more appropriate patient stratification in clinical trials and may improve disease management and treatment outcome.

Materials and Methods

This retrospective study was approved by the Memorial Sloan-Kettering Cancer Center (MSKCC) Institutional Review Board. Data were extracted from the Department of Neurology and the Melanoma Disease Management Team database. All patients were seen at MSKCC between January 1991 and December 2001, but may not have received treatment there. Patients were excluded from the analysis if medical records were incomplete; patients not treated at MSKCC were included only if sufficient information was available about their disease history. Patients with American Joint Committee on Cancer (AJCC) stage IV melanoma (any T, any N, M1a, M1b, M1c: distant skin, lymph node, lung, or visceral metastases)[18] and a BM at any time after diagnosis of melanoma and until death were included. Medical records were reviewed for the following: patient age at diagnosis of stage IV disease, gender, and race; date of initial melanoma diagnosis and AJCC stage at diagnosis; date of diagnosis of stage IV melanoma; systemic therapy (chemotherapy, biologic therapy, and/or immunotherapy) before and after stage IV diagnosis; number of treatments after diagnosis of stage IV disease; presence of BM at or after diagnosis of stage IV disease; presence and type of neurologic symptoms at diagnosis of BM; number of BM; evidence of hemorrhage; hydrocephalus; concomitant leptomeningeal metastases (LM); status of extracranial metastases; type of treatment for BM; and overall survival. Radiographic findings were based primarily on MRI and CT reports; films were reviewed if there was a radiographic question and they were available.

These factors were analyzed for correlation with overall survival using univariate and multivariate Cox regression models.[19] Survival curves were estimated using the Kaplan-Meier method.[20]

Results

Patient and Disease Characteristics

We identified 1,114 patients with AJCC stage IV melanoma, of whom 355 had one or more BM. Table 1 summarizes patient and disease characteristics for the 355 patients (217 men and 138 women) who were analyzed. Patients included in this analysis were treated at MSKCC between 1991 and 2001 in an era when brain MRI was the standard imaging modality. Median age at diagnosis of stage IV melanoma was 52.6 years (range, 9–85 years), and 66% of patients had AJCC stage I or II melanoma[18] at initial diagnosis. Brain metastases were present at diagnosis of stage IV disease in 49% of patients, and the remaining 51% developed BM at a median of 7 months (range, <1 to 52 months) after stage IV diagnosis. The median time from initial diagnosis of cutaneous melanoma to development of BM was 2.7 years (range, 0–31.5 years). Median survival time from detection of BM was 5.2 months (range, 0.1–155 months). Median follow-up among surviving patients was 18.4 months (range, 0.23–155 months), and 92% of patients were deceased at the time of this analysis.

The majority (67%) of patients presented with neurologic symptoms at diagnosis of BM. Radiographic imaging revealed that 88% of patients had parenchymal BM, 2% had LM, 9% had both, and the type of intracranial metastases was not described for 1% of patients (Table 1). At the time of BM diagnosis, 83% of patients had extracranial metastases. Approximately one-third of patients had intratumoral hemorrhage. Of the 107 patients with evidence of intratumoral hemorrhage on MRI at initial diagnosis, 88 (82%) had neurologic symptoms (seizure in 19 and other neurologic symptoms in 69). Among patients with hydrocephalus (n = 26), 10 (38%) had radiographic evidence of LM. Among the 40 patients with LM, 7 (18%) had no parenchymal BM, 3 (8%) had one lesion, 8 (20%) had two or three lesions, and 22 (55%) had four or more lesions.

Treatment

Before the diagnosis of BM, 30% of patients had received systemic therapy for melanoma (Table 2). At some point after the diagnosis of melanoma, 82% of patients had received systemic therapy, and 76% of the 355 patients had received chemotherapy (specifically, 32% of the 355 patients received temozolomide). Among 106 patients treated with temozolomide beginning in 1999, at least 52 (49%) patients received a dose-dense regimen consisting of 75 mg/m^2/day continuously for 6 weeks every 8-week cycle, as opposed to the standard 5-day regimen (150–200 mg/m^2 × 5 days every 28-day cycle). Temozolomide was not used in conjunction with radiation therapy.

Table 1. Patient and disease characteristics ($n = 355$)

	n	%
Gender		
Male	217	61.1
Female	138	38.9
AJCC stage at melanoma diagnosis		
I–II	233	65.6
III	64	18.0
IV	58	16.3
Race		
Caucasian	349	98.3
Hispanic	5	1.4
African American	1	0.3
Brain metastasis at diagnosis of stage IV		
No	181	51.0
Yes	174	49.0
Neurologic symptoms at diagnosis of brain metastasis		
Asymptomatic	116	32.7
Focal	107	30.1
Nonfocal	88	24.8
Seizures	39	11.0
Unknown	5	1.5
Extracranial metastasis at diagnosis of brain metastasis		
No	57	16.1
Yes	296	83.4
Unknown	2	0.5
Parenchymal metastasis		
No	7	2.0
Yes	346	97.5
Unknown	2	0.5
Number of parenchymal brain metastases		
0	7	2.0
1	128	36.1
2–3	85	23.9
⩾4	130	36.6
Unknown	5	1.4
Hemorrhagic brain metastasis		
Yes	123	34.6
No	219	61.7
Unknown	13	3.7
Leptomeningeal metastasis		
Yes	40	11.3
No	315	88.7
Hydrocephalus		
Yes	26	7.3
No	313	88.2
Unknown	16	4.5
Lung metastasis		
Yes	201	56.6
No	154	43.4
Visceral/bone metastasis		
Yes	135	38.0
No	220	62.0
Lymph node/soft tissue metastasis		
Yes	190	53.5
No	165	46.5

Abbreviation: AJCC, American Joint Committee on Cancer.

Table 2. Treatment ($n = 355$)

Modality	*n*	%
Systemic treatment before stage IV diagnosis		
Yes	108	30.4
No	237	66.8
Unknown	10	2.8
Surgical resection (i.e., craniotomy)		
Yes	126	35.5
No	229	64.5
Whole-brain radiotherapy		
Yes	190	53.5
No	154	43.4
Unknown	11	3.1
Radiosurgery		
Yes	78	22.0
No	275	77.4
Unknown	2	0.5
Number of systemic therapies for stage IV disease		
0	72	20.3
1	130	36.6
2	72	20.3
3	65	18.3
Unknown	16	4.5
Chemotherapy ever		
No	71	20.0
Yes	268	75.5
Unknown	16	4.5
Chemotherapy for stage IV disease		
No	82	23.1
Yes	256	72.1
Unknown	17	4.8
Systemic treatment ever		
No	50	14.1
Yes	290	81.7
Temozolomide treatment ever		
No	236	66.5
Yes	113	31.8
Unknown	6	1.7

Nonchemotherapy treatment of BM consisted of surgery, WBRT, or RS. It is important to note that treatment with these modalities was on a continuum; therefore, order and timing were not standardized among patients, thereby limiting the interpretation of the impact of these treatments on survival outcome. Of the 126 (36%) patients who had surgery, 76 (60%) had a single lesion, 30 (24%) had two or three lesions, and 19 (15%) had four or more lesions. Of the 49 patients with one or more BM who underwent surgery, 19 had evidence of hemorrhage on MRI at initial diagnosis, 4 presented with seizure, and 21 presented with neurologic symptoms. The majority of these patients underwent surgery for symptom control. Five other patients developed hemorrhage and/or neurologic symptoms after the diagnosis of BM and underwent surgery at that time. Surgical resection was combined with other treatment modalities in 90 (25%) of

355 patients and was the only treatment in 36 (10%) of 355 patients. WBRT was administered to 190 (54%) patients; it was combined with other modalities in 90 (25%) patients and was the only treatment in 100 (28%) patients. The median and most common dose was 3,000 cGy (range, 400–5,000 cGy). RS was used in 78 (22%) patients; it was combined with other modalities in 52 (15%) patients and was the only treatment in 26 (7%) patients. Of the 78 patients treated with RS, 35 (45%) had one lesion, 35 (45%) had two or three lesions, and 6 (8%) had four or more lesions. The median dose was 1,850 cGy (range, 1,350–3,750 cGy), and the most common doses were 1,800 cGy and 2,100 cGy.

Univariate Analysis

In the univariate analysis, of the 12 patient or disease characteristics assessed, 7 were associated with significantly shorter survival, including age > 65 years, presence of extracranial metastases, presence of BM at stage IV diagnosis, presence of neurologic symptoms at diagnosis of BM, four or more BM, hydrocephalus, and LM (Table 3).

Table 3. Univariate results: overall survival by patient and disease characteristics

Factor	*n*	Median	95% CI	Log-Rank *p* Value
Age, years				
⩽65	263	6.2	5.2, 6.9	0.0044
>65	92	3.3	2.6, 5.1	
Gender				
Female	138	5.2	4.3, 6.5	0.3575
Male	217	5.9	4.3, 6.9	
Extracranial disease				
No	57	10.0	7.3, 13.8	0.0002
Yes	296	5.0	4.1, 6.0	
Brain metastasis at diagnosis of stage IV disease				
No	181	12.5	10.4, 14.4	0.0099
Yes	174	8.3	6.9, 9.4	
Neurologic symptoms				
Asymptomatic	116	7.4	6.6, 9.4	0.0227
Symptomatic	234	4.3	4.0, 5.2	
Number of brain metastases				
1–3	213	8.0	6.6, 9.5	<0.0001
⩾4	130	3.3	2.6, 4.0	
Hydrocephalus				
No	313	5.9	4.8, 6.7	0.0005
Yes	26	3.8	1.7, 5.1	
Leptomeningeal metastasis				
No	315	6.0	5.0, 6.7	0.0004
Yes	40	4.0	2.5, 5.2	
Hemorrhagic lesion				
No	219	5.2	4.1, 6.2	0.8551
Yes	123	6.0	4.8, 8.0	
Parenchymal metastasis				
No	7	1.3	0.8, 6.1	0.0055
Yes	346	5.7	4.8, 6.6	
AJCC stage at initial diagnosis				
I–II	233	5.9	5.0, 6.7	0.7855
III	64	3.2	2.7, 6.7	
IV	58	6.1	4.6, 8.7	
Brain metastasis only				
No	291	5.0	4.1, 5.9	0.0003
Yes	64	9.7	6.7, 13.0	
EC metastasis and age, years				
No EC metastasis, age ⩽ 65	40	10.2	7.9, 14.7	<0.0001
No EC metastasis, age > 65	17	8.3	3.1, 15.1	
EC metastasis, age ⩽ 65	221	5.3	4.4, 6.5	
EC metastasis, age > 65	75	2.9	1.9, 4.3	

Abbreviations: CI, confidence interval; AJCC, American Joint Committee on Cancer; EC, extracranial.

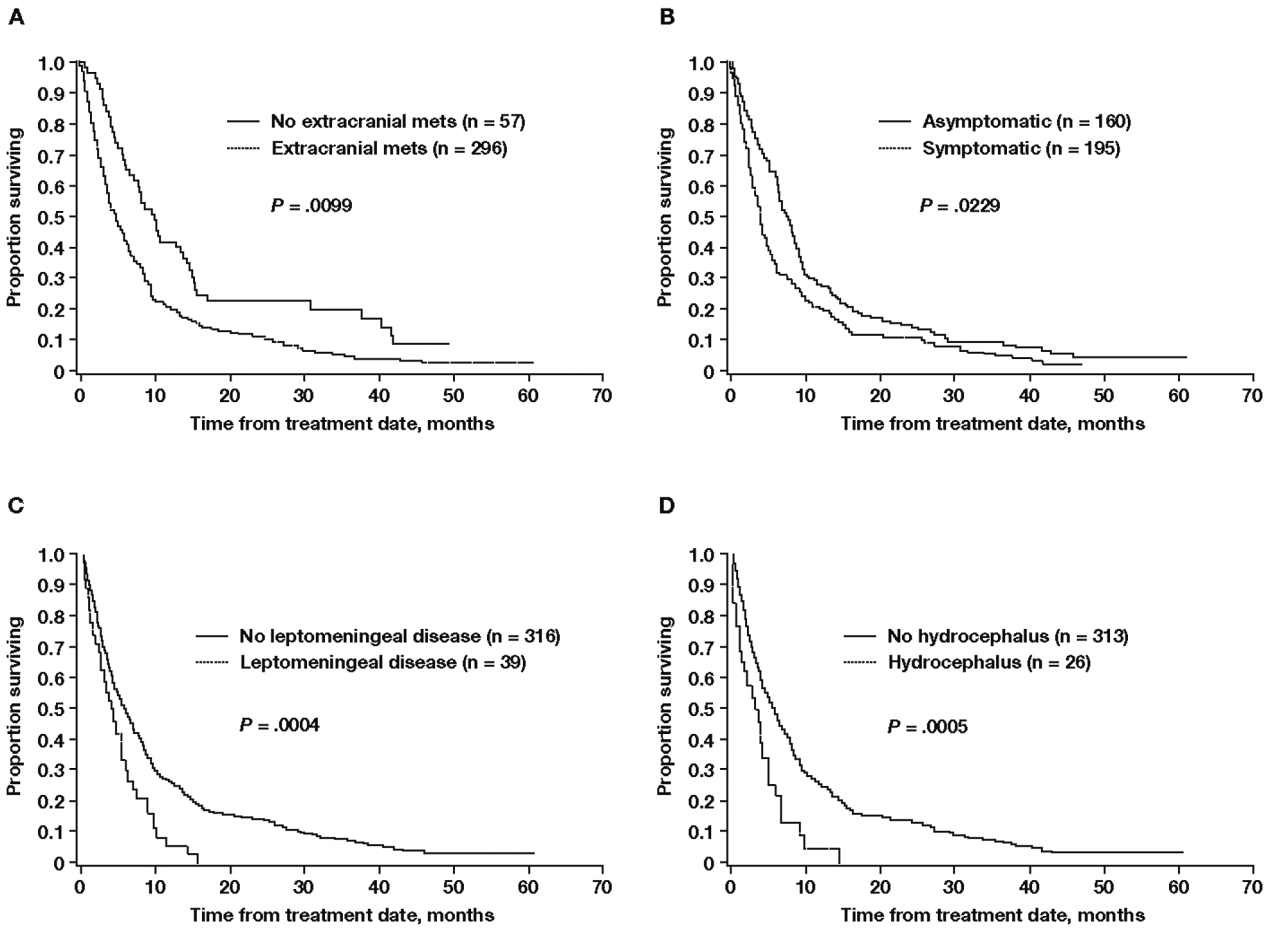

Fig. 1. Kaplan-Meier estimate of survival for patients with or without extracranial metastases (A), with or without neurologic symptoms (B), with or without leptomeningeal metastases (C), and with or without hydrocephalus (D). Abbreviation: mets, metastases.

Survival curves for patients with or without extracranial metastases, neurologic symptoms, LM, or hydrocephalus are shown in Fig. 1.

Univariate analysis showed that patients treated with temozolomide (either for systemic melanoma or for BM) and those receiving surgery or RS for the treatment of BM had longer survival (Table 4). Median survival was 8 months for patients treated with temozolomide compared with 4 months if not treated with temozolomide ($p = 0.0009$) (Table 4). Because temozolomide became commercially available only in 1999, the majority of patients in this cohort were not treated with temozolomide. Among patients who had surgical resection of BM, median survival was 9 months compared with 4 months for those who did not ($p < 0.0001$) (Table 4). Likewise, patients who received RS had a median survival of 10 months compared with 4 months for patients who did not ($p < 0.0001$) (Table 4). Patients treated with WBRT had a median survival of 4 months compared with 2 months for patients who received no treatment for BM. Outcomes based on treatment (either single modality or combination) are listed in Table 5.

Multivariate Analysis

Multivariate analysis demonstrated that four of the seven patient or disease characteristics were associated with shorter survival, including age > 65 years, presence of extracranial metastases, presence of neurologic symptoms at diagnosis of BM, and having four or more BM (Table 6). In addition, patients treated with surgery, RS, temozolomide, or systemic therapy at any time during the course of disease had the longest survival. As indicated, these treatments may have been used at any point after the diagnosis of BM, so the true benefit cannot be determined by this analysis.

Discussion

Our goal was to identify prognostic factors for survival in patients with stage IV melanoma and BM. Some prognostic factors have previously been reported for this population.[3,6,9] However, the present analysis is based on a more contemporary patient population, and the findings are unique in several respects compared to previous reports. We selected 1991 as the start date for this study because brain MRI scan became the standard imaging modality for BM at about that time, whereas

Table 4. Univariate analysis: overall survival when one brain-metastasis-directed treatment was part of care

Treatment	*n*	Median
Surgical resection		
No	229	3.9
Yes	126	9.3
Radiosurgery		
No	275	4.3
Yes	78	10.0
Temozolomide		
No	236	4.1
Yes	113	7.9
Whole-brain radiotherapy		
No	154	4.5
Yes	190	6.1
Systemic therapy ever		
No	50	3.6
Yes	290	5.8
Chemotherapy ever		
No	71	4.3
Yes	268	5.9

Table 5. Survival when one or more treatments of brain metastases were part of care ($n = 355$)

Treatment	*n*	%	Median Survival (Months)
None	83	23.3	2.04
WBRT alone	100	28.2	3.98
RS alone	26	7.3	9.87
Surgery alone	36	10.1	8.16
WBRT + RS	20	5.6	9.44
Surgery + WBRT	58	16.3	8.81
Surgery + RS	20	5.6	13.75
Surgery + WBRT + RS	12	3.4	10.2

Abbreviations: WBRT, whole-brain radiotherapy; RS, radiosurgery.

Table 6. Multivariate analysis: overall survival

Factor	Risk ratio	95% CI	*p* Value
Variable			
Age > 65 years	1.53	1.17, 1.99	0.0017
Extracranial metastases	2.13	1.52, 2.98	<0.0001
Neurologic symptoms	1.64	1.26, 2.12	0.0002
Number of brain metastases (1–3 vs. ⩾4)	1.85	1.39, 2.46	<0.0001
Treatment as part of care			
Surgical resection	0.56	0.43, 0.75	<0.0001
Radiosurgery	0.69	0.50, 0.94	0.0191
Temozolomide	0.69	0.53, 0.88	0.0034
Systemic treatment ever	0.70	0.49, 1.01	0.0538

Abbreviation: CI, confidence interval.

earlier studies used head CT scans or autopsy results. Similar to previous studies, the present study was retrospective, and although patients received a wide variety of treatments and extracranial disease was variable, the outcomes of the regression analysis are similar to those of previous reports. Patients in the present analysis were similar to those included in published studies, although median age was slightly older.[1,2,5–7,10–13,15,21–23] In most respects, the survival outcomes in this series are consistent with published studies. The reported median time from diagnosis of melanoma (AJCC stage I or II)[18] to BM is 1.4–4 years,[1,3,5,8,9,11,12] which is consistent with the median of 2.7 years that we observed. In the present study, median survival from diagnosis of BM was 5.2 months overall and 8.3 months in patients with BM at diagnosis of stage IV disease, similar to results from other series. The reported median survival from diagnosis of stage IV melanoma regardless of disease site is 1–24 months,[2,10,24] but patients who develop BM early have a shorter median survival than those who develop BM later.[24]

Only 16% of patients in the present analysis did not have extracranial metastases, and this factor greatly affected survival in both univariate and multivariate analyses, consistent with other studies.[1,3,6,7,9,15] More than half of the patients in the present study had lung, lymph node, or subcutaneous involvement, and about 40% had visceral or bone metastases. In a retrospective analysis of palliative WBRT reported by Morris et al.,[23] patients without extracranial disease had a median survival of 3.5 months versus 1.1 months for patients with extracranial metastases, and the number of extracranial metastatic sites correlated inversely with survival. Similarly, in the present study, median survival was 10 months for patients with BM only versus 5 months for patients with concurrent extracranial metastases. These data suggest that extensive extracranial metastases are associated with a decrease in survival. However, the cause of death was not documented in our database, so we are unable to comment on whether death was from a neurologic or systemic cause. We can infer that patients with only BM died a neurologic death, whereas those with BM and systemic disease likely died due to systemic and brain progression.

The results of the present analysis are also consistent with the Radiation Therapy Oncology Group recursive partitioning analysis (RPA) classification for patients with BM based on Karnofsky performance status (< or ⩾ 70%), age (< or ⩾ 65 years), and status of extracranial disease (controlled or uncontrolled).[25,26] When the RPA classification was applied to patients with BM from melanoma, median survival was 5–10 months for class I, 2.5–5.9 months for class II, and 0.75–2.5 months for class III.[4,7,23] In the present analysis, although information on Karnofsky performance status was not routinely available, outcome based on age and extracranial metastases demonstrated a median survival of 10 months for patients ⩽ 65 years of age with no extracranial metastases (similar to RPA class I) and 3 months for patients > 65 years of age with extracranial metastases (similar to RPA class III) (Table 4).

Our analysis has also confirmed that neurologic symptoms at diagnosis of BM are significant predictors of shorter survival.[14,16,27] Interestingly, intratumoral hemorrhage had no significant effect on survival in the present analysis. Although hemorrhage can be fatal, in our series, these patients lived slightly longer than patients without hemorrhage, possibly because of earlier detection of BM. The majority of patients with hemorrhage underwent surgical resection for symptom relief regardless of the total number of BM. Intratumoral hemorrhage has been reported to occur in 29% to 40% of melanoma patients with BM based on imaging studies[12,13,16] and in up to 50% of patients by pathologic review.[28] In one series, hemorrhage was the cause of death in 20% of patients.[2]

Hydrocephalus was noted in 26 (7%) patients, and 10 of these patients also had LM on imaging. Patients with hydrocephalus had significantly shorter median survival compared with those who did not (4 vs. 6 months), possibly due to LM not seen on imaging and not accounted for by a posterior fossa BM. Leptomeningeal disease was also a significant negative prognostic factor in the univariate analysis but not in the multivariate analysis. LM was observed in 40 (11%) patients based on MRI findings, which undoubtedly underestimates the true incidence. The combination of LM and BM has been reported to be a significant adverse prognostic factor despite treatment with WBRT.[16,23] In our series, LM was correlated with an increased number of parenchymal lesions, which may explain why LM was a significant prognostic factor on univariate analysis.

Number of BM was one of the strongest prognostic factors in both univariate and multivariate analyses. Median survival decreased from 8 months in patients with one to three lesions to only 3 months for patients with four or more lesions. This finding may account for the poor prognosis associated with melanoma BM, because up to 86% of patients have multiple lesions at diagnosis,[2,3,6–9,11,13,22] and survival has been shown to decrease inversely with increased number of BM and increased tumor burden.[3,4,9,12,22] However, in the present study, the outcome for patients with two or three lesions was not worse than for patients with one lesion. This may reflect recent improvements in surgical and RS techniques.

Our data on treatment suggest that BM-directed therapies do improve survival outcomes compared with supportive care only, similar to data from other reports.[3,6,29] Patients treated with surgery and RS as part of BM-directed therapy had the longest survival. However, a selection bias most certainly contributed to this result, in that patients treated with surgery and/or RS likely had a lower intracranial tumor burden and controlled or absent extracranial disease and were likely healthier overall compared with patients receiving WBRT or supportive care. Patients with better RPA class do better than others, confirming the fact that having fewer "negative" factors leads to better outcomes. Meier et al.[22] reported that all treatments for BM, including WBRT, had a significant positive effect on survival. However, the benefit of WBRT continues to be debated. Our data suggest that WBRT alone for melanoma BM provided only a marginal survival benefit over no therapy for BM. Some authors have suggested that WBRT may delay central nervous system progression by up to fourfold[3,5,14,21] and may delay development of LM.[21] Therefore, in select patients, WBRT may provide some benefit. For example, it has been suggested that patients with limited or no extracranial metastases may have improved survival when treated with WBRT after surgery.[3,5,6,14,21] Hagen et al.[21] reported that patients who had resection of a single BM had a median survival of 6.4 months, which was increased to 8.3 months in patients who received adjuvant WBRT. In general, patients with a single BM and no extracranial metastases appear to benefit the most from aggressive local treatment of BM. The degree of surgical resection for a given lesion has also been shown to correlate with survival,[10,12,14] and a second surgical resection can further improve survival.[16]

Several reports have also demonstrated the important role of RS in the management of melanoma BM, yielding good disease control rates and median survivals between 7 and 9 months.[9,15,17,30,31] Seung et al.[31] reported similar median survivals whether a single or multiple lesions were treated (~8 months), and median time to development of new BM was approximately 6 months. The role of WBRT in conjunction with RS is controversial. Some studies have shown that WBRT may decrease development of new BM,[9] whereas other studies have not.[17,30,32] In patients with a single BM, RS achieves excellent disease control, and median survivals up to 22 months have been reported without use of WBRT.[15] The Eastern Oncology Cooperative Group found a median survival of 8.3 months for patients treated with RS alone for radioresistant BM (renal cell cancer, melanoma, and sarcoma), with no difference in outcome based on histology.[33] Their survival data are similar to ours, but they did have a 50% failure in the brain at 6 months, suggesting that RS alone be used in select cases.

The data for systemic chemotherapy for the treatment of BM are limited and show that it is largely ineffective, with median survivals of 3–4.5 months.[34,35] Recent studies have shown that temozolomide induced objective responses in patients with BM when used as a single agent or in combination with thalidomide or docetaxel.[36–40] Meier et al.[22] also reported that chemotherapy, including treatment with temozolomide, prolonged survival in patients with melanoma BM, and Paul et al.[41] demonstrated that temozolomide significantly decreased the incidence of BM compared with dacarbazine when used as primary therapy for stage IV melanoma. In our analysis, the use of temozolomide appeared to improve survival, but further studies are needed to confirm this finding as well as define the optimal dose, schedule, and combinations for the treatment of BM.

In summary, the present analysis confirmed many of the prognostic factors previously reported by others and defined additional new factors. These data can be used to optimize patient care and to guide selection and stratification of patients in future clinical trials. The retrospective nature of this study limits what can be inferred about individual therapies, as timing of treatment was

variable and response rates and time to progression were not consistently documented. Despite these limitations, our survival data are similar to those published in the literature. We recommend that aggressive treatment be used for patients with limited or no extracranial disease and for those with one to three BM. In these patients, surgery or RS, alone or in combination, may have the greatest impact on survival. However, the majority of melanoma patients present with multiple BM and extensive concurrent extracranial disease. For patients with four or more BM, treatment with RS, with or without WBRT, may be an alternative approach, as WBRT alone appears to provide only marginal benefit. Patients with hemorrhage or neurologic symptoms who will likely survive for at least a few months should receive palliative surgery. Temozolomide has been shown to be an active agent in BM from melanoma and should be considered as part of therapy for these patients. Use of the RPA classification should help to determine the appropriate level of aggressiveness, and the prognostic index devised by Morris et al.[23] may be helpful for stratifying RPA class II patients. Ultimately, treatment decisions must be tailored to the individual patient, and a clear understanding of patient and disease characteristics that influence survival prognosis can be extremely helpful for determining the best treatment approach.

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