Original Article

Melanoma Brain Metastasis Presentation, Treatment, and Outcomes in the Age of Targeted and Immunotherapies

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BACKGROUND: Historically, the prognosis for patients who have melanoma brain metastasis (MBM) has been dismal. However, breakthroughs in targeted and immunotherapies have improved long-term survival in those with advanced melanoma. Therefore, MBM presentation, prognosis, and the use of multimodality central nervous system (CNS)-directed treatment were reassessed. **METHODS:** In this retrospective study, the authors evaluated patients with MBM who received treatment at Memorial Sloan Kettering Cancer Center between 2010 and 2019. Kaplan-Meier methodology was used to describe overall survival (OS). Recursive partitioning analysis and time-dependent multivariable Cox modeling were used to assess prognostic variables and to associate CNS-directed treatments with OS. **RESULTS:** Four hundred twenty-five patients with 2488 brain metastases were included. The median OS after an MBM diagnosis was 8.9 months (95% CI, 7.9-11.3 months). Patients who were diagnosed with MBM between 2015 and 2019 experienced longer OS compared to those who were diagnosed between 2010 and 2014 (OS, 13.0 months [95% CI, 10.47-17.06 months] vs 7.0 months [95% CI, 6.1-8.3 months]; $P = .0003$). Prognostic multivariable modeling significantly associated shortened OS independently with leptomeningeal dissemination ($P < .0001$), increasing numbers of brain metastases at diagnosis ($P < .0001$), earlier MBM diagnosis year ($P = .0008$), higher serum levels of lactate dehydrogenase ($P < .0001$), receipt of immunotherapy before MBM diagnosis ($P = .003$), and the presence of extracranial disease ($P = .02$). The use of different CNS-directed treatment modalities was associated with presenting symptoms, diagnosis year, number and size of brain metastases, and the presence of extracranial disease. Multivariable analysis demonstrated improved survival for patients who underwent craniotomy ($P = .01$). **CONCLUSIONS:** The prognosis for patients with MBM has improved within the last 5 years, coinciding with the approval of PD-1 immune checkpoint blockade and combined *BRAF/MEK* targeting. Improving survival reflects and may influence the willingness to use aggressive multimodality treatment for MBM. ***Cancer* 2021;127:2062-2073**.

LAY SUMMARY:

- Historically, melanoma brain metastases (MBM) have carried a poor survival prognosis of 4 to 6 months; however, the introduction of immunotherapy and targeted precision medicines has altered the survival curve for advanced melanoma.
- In this large, single-institution, contemporary cohort, the authors demonstrate a significant increase in survival of patients with MBM to 13 months within the last 5 years of the study.
- A worse prognosis for patients with MBM was significantly associated with the number of metastases at diagnosis, previous exposure to immunotherapy, spread of disease to the leptomeningeal compartment, serum lactate dehydrogenase elevation, and the presence of extracranial disease.
- The current age of systemic treatments has also been accompanied by shifts in the use of central nervous system-directed therapies.

KEYWORDS: brain metastases, immunotherapy, melanoma, survival, targeted therapy.

INTRODUCTION

Melanoma is one of the primary causes of malignant metastases to the central nervous system (CNS), accounting for 6% to 12% of all metastatic brain tumors.[1-3] Survival after a diagnosis of melanoma brain metastasis (MBM) has historically been dismal, with an overall survival (OS) of 4 to 6 months.[4-8] However, over the recent decade, numerous advances have been made in targeted therapy for melanoma, such as BRAF and MEK inhibition, and in immunotherapy with approval of the checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab.[9] These advances have resulted in significant improvements in the OS of patients with metastatic melanoma.[10-18] Furthermore, it has been demonstrated that patients with MBM also respond to these therapies.[19-24] In the COMBI-MB trial (ClinicalTrials.gov identifier NCT02039947), 58% of patients who had BRAF V600E-positive MBM responded

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to combination dabrafenib and trametinib,[23] and the combination of nivolumab and ipilimumab produced intracranial responses in 46% to 56% of patients with MBM.[22,24] Although clinical trials have begun to include more patients with MBM, little data exist to assess how current treatments have changed the overall prognosis of MBM diagnosis, affected central nervous system (CNS)-directed local treatment algorithms with surgery and radiation, or enumerated factors that may inform the survival of patients with MBM. Notably, the most recent iteration of the Graded Prognostic Assessment tool called the Melanoma-molGPA demonstrated the prognostic value of clinical features, including age, Karnofsky performance status, the number of CNS metastases, the presence of extracranial metastases, and BRAF status, in a cohort identified through 2015; however, leptomeningeal disease (LMD) and the contribution of immunotherapy were not investigated.[25] This large, retrospective, single-institution study describes the presentation, treatments, and survival of patients with MBM in the contemporary immunotherapy and precision medicine era.

MATERIALS AND METHODS

This study was approved by the Memorial Sloan Kettering Cancer Center (MSK) Institutional Review Board. Patients (n = 440) were identified by an institutional database search for all patients, regardless of treatments, with a diagnosis of cutaneous melanoma, no other systemic malignancy, and brain metastases (BMs) diagnosed from January 2010 through January 2019. Patients were excluded from the analysis if they had primary LMD without parenchymal metastases at time of MBM diagnosis (n = 4) or if medical records had incomplete clinical documentation for the parameters enumerated below, represented a single encounter without any follow-up, or were without baseline or follow up imaging (n = 11). A retrospective chart review was conducted to identify demographics, including age at diagnosis of MBM; the number, size, and location of BMs at diagnosis; CNS symptoms at diagnosis; the presence of metastasis-associated hemorrhage; serum lactate dehydrogenase (LDH) level at MBM diagnosis; the presence or absence of extracranial disease on the computed tomography scan of the chest, abdomen, and/or pelvis most contemporaneous to the time of BM diagnosis; diagnosis of LMD and/or hydrocephalus during treatment; OS; systemic and CNS-directed treatments before and after BM diagnosis (chemotherapy, immunotherapy, targeted *BRAF/MEK* therapy, stereotactic and/or whole brain radiation, and surgery, including craniotomy and/or cerebrospinal fluid diversion); and the presence of progressive systemic and/or CNS disease at the time of death (if known). Radiographic findings were based on radiologist interpretations of magnetic resonance imaging and computed tomography studies; these were further reviewed when quantitative or qualitative features of interest (size, number, location, hydrocephalus) were not commented upon. The presence of hemorrhage in metastases was based on radiology reports. Dominant metastasis was defined as the largest metastasis present on imaging, and size was determined based on greatest axial/coronal/sagittal dimension.

Statistical Analysis

Descriptive statistics, such as frequencies, means, and SDs, were used to characterize the cohort under study. OS was defined as the time from MBM diagnosis until the date of death or the date of last follow-up for patients who were censored. Recursive partitioning analysis was used for exploration and visualization of empirically identified cutoffs for associations of the number of BMs, the MBM diagnosis year, and the size of largest MBM with OS. Univariable and multivariable Cox modeling was used to associate variables of interest with OS. Variables that were significant in the univariable models were brought forward for evaluation in the multivariable analysis. LMD and all treatments after a diagnosis of MBM were treated as time-dependent variables in the Cox models. The time-dependent Cox models associating LMD with OS were stratified by variables of interest, and heterogeneity was tested with nested models using the likelihood ratio test. Kaplan-Meier methodology was used to display survival curves. The cumulative incidence of LMD after a diagnosis of BM was calculated using competing risks methodology, and the Gray test was used to compare cumulative incidence curves stratified by pre-BM immunotherapy. The Kruskal-Wallis test was used to investigate the association between presenting MBM symptoms and the dominant size and number of BMs. The Fisher test was used to explore the association of presenting MBM symptoms with dominant MBM location. The Wilcoxon 2-sample test was used to investigate the association between pre-BM diagnosis immunotherapy and the number of BMs at diagnosis. A cause-specific, time-dependent Cox model was used to model the association of variables of interest with post-MBM

treatments. All *P* values were 2-sided, with a level of statistical significance <.05. To summarize our work, we emphasized *statistically significant* findings, ie, those with *P* values below the threshold of .05. Without a power calculation, we lacked information about the magnitude of the association(s) that could be detected with high probability for our study design. We also have presented estimates of the association and their confidence intervals and suggest that these results add value to the interpretation, both for findings with *P* < .05 and for those with larger *P* values. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.6.0 (R Foundation for Statistical Computing).

RESULTS

Demographics, Survival, and BM Presentation

Four hundred twenty-five patients were diagnosed with a total of 2488 MBMs at MSK between 2010 and 2019 (Table 1). The mean patient age was 59.3 years, and there was a male predominance (men, 72%; women, 28%). There were 324 deaths over the study duration. The median OS from the diagnosis of BMs was 8.9 months (95% CI, 7.9-11.3 months) (Fig. 1). The median follow-up was 22.5 months for survivors. The 3-year OS rate for the cohort was 19.4% (95% CI, 15.5%-24.1%), and the 5-year OS rate was 13.6% (95% CI, 10.0%-18.6%). Forty-nine percent of patients (n = 206) had a BRAF mutation identified by immunohistochemistry, mass spectrometry, and/or targeted sequencing, whereas 43% had wild-type BRAF, and 8% had unknown BRAF status. Eighty-eight percent of patients had extracranial disease present at MBM diagnosis, 10% had BMs only without evidence of extracranial disease, and 2% had unknown BM status. The median number of parenchymal metastases at BM diagnosis was 3 (interquartile range, 1-6 parenchymal metastases; range, from 1 to >50 parenchymal metastases). In 90% of patients, the dominant/largest BM was located in the supratentorial compartment compared with the infratentorial compartment in 10%. The median size of the dominant BM was 1.8 cm (interquartile range, 0.9-2.9 cm; range, 0.2-8.8 cm). Fifty-eight percent of patients had radiographic hemorrhage present at BM diagnosis, and 72% had hemorrhage present by the last follow-up. Serum LDH levels at the time of MBM diagnosis were above normal limits in 23%, within normal limits for 32%, and unknown for 45% of patients. Supporting Figure 1 illustrates the cumulative incidence of LMD diagnosis

TABLE 1. Melanoma Brain Metastasis Cohort Characteristics

Variable	No. of Patients (%)
Age at melanoma Dx—continuous, y	425 (100)
Mean	56.6
Median	58.8
Range	15.2-91.8
Age at BM Dx—continuous, y	425 (100)
Mean	59.3
Median	61.3
Range	18.9-92.4
No. of BM at Dx—continuous	425 (100)
Mean	5.9
Median	3.0
Range	1.0 to >50.0
Dominant BM size—continuous, cm	425 (100)
Mean	2.1
Median	1.8
Range	0.2-8.8
Serum LDH value (U/L)—continuous	233 (55)
Mean	389.1
Median	221
Range	110.0-4970.0
Sex	
Women	121 (28)
Men	304 (72)
BRAF status	
Wild type	184 (43)
Mutated	206 (49)
Unknown	35 (8)
Systemic burden	
No extracranial disease	42 (10)
Extracranial disease present	372 (88)
Unknown	11 (3)
Presenting symptoms	
Asymptomatic	166 (39)
Headache	72 (17)
Motor/sensory	83 (20)
Seizure	34 (8)
Mental status change	56 (13)
Other	14 (3)
Serum LDH (U/L)	
Within normal limits	134 (32)
Above normal limits	99 (23)
Unknown	192 (45)
Hemorrhage present in BM at diagnosis	
No	177 (42)
Yes	248 (58)
Hemorrhage present in BM at last follow-up	
No	119 (28)
Yes	306 (72)
Dominant BM location	
Frontal	162 (38)
Temporal	62 (15)
Parietal	80 (19)
Occipital	43 (10)
Cerebellar/pontine	44 (10)
Subcortical	34 (8)
Dominant BM supratentorial/infratentorial	
Supratentorial	381 (90)
Infratentorial	44 (10)
Hydrocephalus	
No	382 (90)
Yes	43 (10)
Cumulative incidence of LMD [95% CI], %	
At 1 y	12.3 [9.1-15.5]
At 3 y	15.33 [11.7-18.9]

TABLE 1. *Continued*

Variable	No. of Patients (%)
Pre-BM immunotherapy	
No	226 (53)
Yes	199 (47)
Pre-BM BRAF-targeted therapy	
No	366 (86)
Yes	59 (14)
Post-BM immunotherapy	
No	97
Yes	326 (77)
Unknown	2 (0)
Post-BM BRAF-targeted therapy	
No	317 (75)
Yes	108 (25)
Surgery	
None	260 (61)
Shunt	7 (2)
Craniotomy	147 (35)
Both	9 (2)
Radiation	
None	92 (22)
SRS	182 (43)
WBRT	103 (24)
Both	48 (11)

Abbreviations: BM, brain metastasis; LDH, lactate dehydrogenase; LMD, leptomeningeal disease; Max, maximum; Min, minimum; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

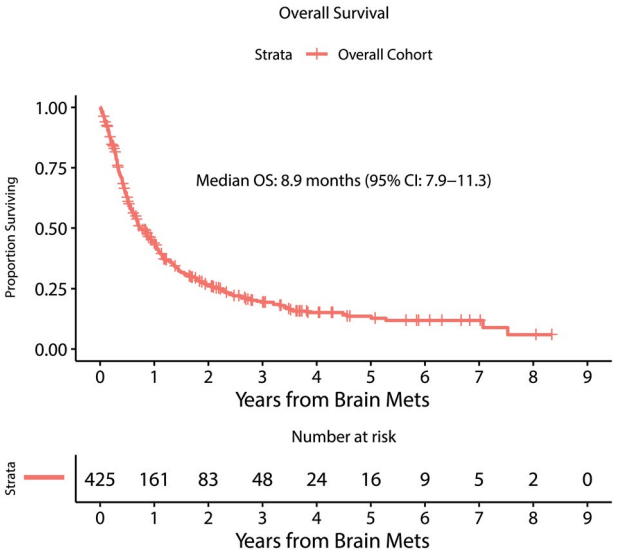

Figure 1. Kaplan-Meier estimates of overall survival (OS) are illustrated from the time of melanoma brain metastases (MBM) diagnosis.

after a diagnosis of MBM, demonstrating a 1-year incidence of 12.3% (95% CI, 9.1%-15.5%) and a plateau in LMD diagnosis by approximately 3 years after an MBM diagnosis, with an overall incidence of 15.3% (95% CI, 11.7%-18.9%) for patients with MBM at 3 years.

Most patients were asymptomatic at the time of BM diagnosis (39%), whereas 20% had focal motor or sensory complaints. Seizure was the initial presenting symptom in 8% of patients, and 33% presented with headache, mental status change, or other neurologic complaint without focal deficit or seizure. Presenting symptoms differed significantly in relation to dominant metastasis size (see Supporting Table 1). Asymptomatic patients had a median dominant BM size of 1.0 cm versus 3.1 cm for patients who presented with headache, 2.2 cm for those who presented with motor/sensory deficit, and 2.6 cm for those who presented with seizure ($P <$ .0001). The dominant BM location was also significantly associated with presenting symptoms ($P = .01$) (see Supporting Table 2). Headache was the most common presentation for patients with cerebellar/pontine BMs, accounting for 34% of those cases. Seizures and motor/sensory deficits occurred more frequently in patients who had frontal and parietal BMs compared with those who had BMs in other locations. The number of BMs present at diagnosis was not significantly associated with presenting symptom.

Prognostic Factors

Recursive partitioning analysis was used to explore the cutoff point associated most with OS for each of the following variables individually: number of MBM at diagnosis, year of MBM diagnosis, and size of the largest MBM (Fig. 2). The analysis demonstrated that <5 versus ≥5 BMs were associated most with OS. The median OS for patients who had <5 BMs was 12.5 months (95% CI, 10.5-16.0 months) versus those who had ≥5 BMs (median OS, 5.5 months; 95% CI, 4.2-6.8 months). This analysis demonstrated that an MBM diagnosis year between 2010 and 2014 versus between 2015 and 2019 was associated most with OS. The median OS for patients who had MBM diagnosed between 2010 and 2014 was 7.0 months (95% CI, 6.1-8.3 months) compared with those who had MBM diagnosed between 2015 and 2019 (median OS, 13.0 months; 95% CI, 10.5-17.1 months). Multivariable hazard ratios (HRs) did not demonstrate a significant difference in the risk of systemic progression (HR, 1.46; 95% CI, 0.89-2.39; $P = .14$) or CNS progression (HR, 1.37; 95% CI, 0.89-2.12; $P = .15$) at the time of death between patients who were diagnosed during 2010 through 2014 and those who were diagnosed during 2015 through 2019. No cutoff point was identified for dominant BM size. The receipt of immunotherapy

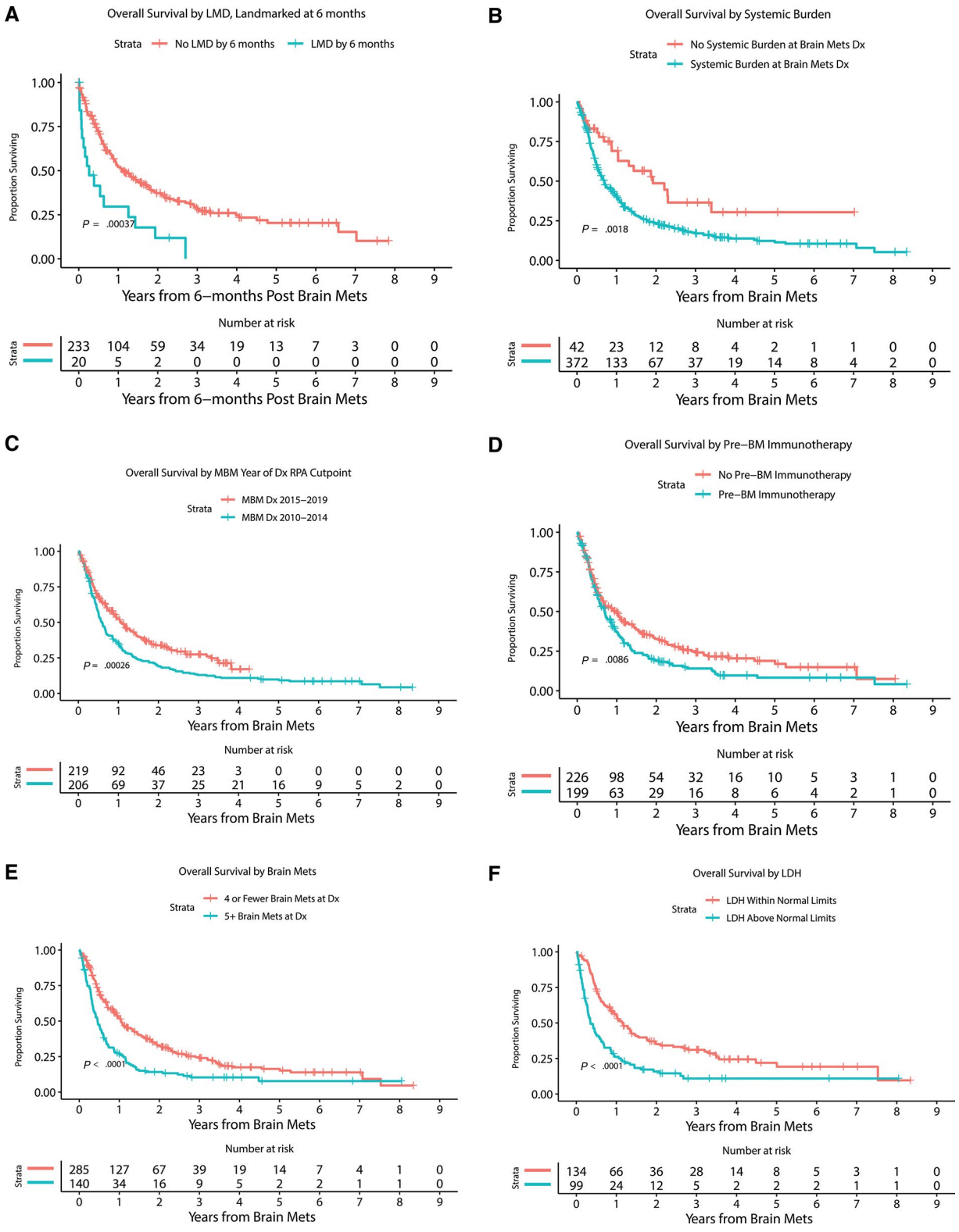

Figure 2. Kaplan-Meier estimates of overall survival are illustrated for patients (A) with or without leptomeningeal disease (LMD) 6 months after a melanoma brain metastases (MBM) diagnosis (Dx), (B) with or without extracranial systemic burden, (C) who had an MBM Dx between 2010 and 2014 or between 2015 and 2019, (D) who did or did not receive immunotherapy before MBM diagnosis, (E) with <5 or ≥5 brain metastases (BM) at MBM diagnosis, and (F) who had serum lactate dehydrogenase (LDH) levels above or within normal limits. RPA indicates recursive partitioning analysis.

TABLE 2. Factors Associated With Overall Survival in Patients With Metastatic Brain Metastasis

Variable	No. of Patients (%)	Unadjusted		Adjusted[a]	
		HR [95% CI]	*P*	HR [95% CI]	*P*
Age at MBM Dx—continuous	425 (100)	1.007 [0.999-1.014]	.08		
Dominant BM size—continuous, cm	425 (100)	0.99 [0.91-1.08]	.84		
Year of MBM Dx—continuous	425 (100)	0.92 [0.87-0.96]	.0004	0.92 [0.87-0.97]	.0008
Serum LDH					
Within normal limits	134 (32)	Ref	Ref		
Above normal limits	99 (23)	2.14 [1.59-2.87]	<.0001	2.14 [1.58-2.88]	<.0001
No. of BM at Dx—continuous	425 (100)	1.03 [1.02-1.04]	<.0001	1.03 [1.01-1.04]	<.0001
Sex					
Female	121 (48)	Ref			
Male	304 (72)	1.00 [0.78-1.27]	.98		
Presenting symptoms					
Asymptomatic	166 (39)	Ref			
Headache	72 (17)	0.90 [0.65-1.23]	.49		
Motor/sensory	83 (20)	1.06 [0.79-1.43]	.70		
Seizure	34 (8)	0.98 [0.63-1.52]	.93		
Mental status change	56 (13)	1.15 [0.82-1.62]	.42		
Other	14 (3)	0.90 [0.44-1.84]	.77		
Hemorrhage present in BM at Dx					
No	177 (42)	Ref			
Yes	248 (58)	1.04 [0.83-1.30]	.73		
LMD					
No	363 (85)	Ref		Ref	
Yes, time-dependent variable	62 (15)	3.59 [2.69-4.78]	<.0001	3.63 [2.71-4.87]	<.0001
BRAF status					
Wild type	184 (43)	Ref			
Mutated	206 (48)	0.98 [0.78-1.23]	.87		
Pre-BM immunotherapy					
No	226 (53)	Ref		Ref	
Yes	199 (47)	1.34 [1.08-1.67]	.0089	1.40 [1.12-1.75]	.003
Systemic burden at BM Dx					
No extracranial disease	42 (10)	Ref		Ref	
Extracranial disease present	372 (88)	1.97 [1.28-3.04]	.002	1.67 [1.07-2.60]	.02

Abbreviations: BM, brain metastases; Dx, diagnosis; HR, hazard ratio; LMD, leptomeningeal disease; Ref, reference category; WBRT, whole-brain radiation therapy.
[a]Variables that were significant in the unadjusted models were brought forward.

before MBM diagnosis was not associated with any significant difference in the number of BMs at diagnosis.

Table 2 and Figure 2 demonstrate univariable and multivariable (adjusted) analyses for prognostic factors and their association with OS. The number of BMs at diagnosis (HR, 1.03; 95% CI, 1.01-1.04; $P < .0001$), the year of MBM diagnosis (HR, 0.92; 95% CI, 0.87-0.97; $P = .0008$), a diagnosis of leptomeningeal dissemination treated as a time-dependent variable (HR, 3.63; 95% CI, 2.71-4.87; $P < .0001$), a serum LDH level above normal limits at diagnosis (HR, 2.14; 95% CI, 1.58-2.88; $P < .0001$), receipt of immunotherapy before the diagnosis of BM (HR, 1.40; 95% CI, 1.12-1.75; $P = .003$), and the presence of extracranial disease at diagnosis (HR, 1.67; 95% CI, 1.07-2.60; $P = .02$) were all statistically significantly associated with OS in a multivariable model. Factors that were not associated with survival included age, sex, dominant metastasis size, the presence of hemorrhage at MBM diagnosis, presenting symptom, and BRAF mutation status.

Because LMD was only rarely present at the time of MBM diagnosis, it was assessed as a time-dependent variable, not at a specific time point, and was 1 of the strongest negative prognostic factors in this cohort. All patients diagnosed with LMD (n = 66) had a median OS of 2.3 months (95% CI, 1.8-3.4 months) from the time of LMD diagnosis. The cumulative incidence of developing LMD (accounting for death as a competing event) is detailed in Supporting Figure 1. The association of LMD with OS was further investigated by stratifying the cohort by age, year of MBM diagnosis, systemic burden, pre-BM immunotherapy, and pre-BM BRAF-targeted treatment for patients who had BRAF mutations (see Supporting Table 3). In all of these stratification analyses, LMD remained a statistically significant negative prognostic factor for all categories, with the exception of patients aged ≤60 years, although the *P* value for heterogeneity was not statistically significant across age categories. Clinical variables potentially associated with developing LMD were also examined (see Supporting Table 4), and only age at

BM diagnosis (HR, 0.98; 95% CI, 0.96-0.997; $P = .02$) retained a significant association in multivariable analysis; patients who received whole-brain radiation therapy (WBRT) before they were diagnosed with LMD were more likely to have an LMD diagnosis (HR, 3.02; 95% CI, 1.71-5.33; $P = .0001$). We note that undergoing craniotomy (HR, 0.95; 95% CI, 0.54-1.68; $P = .86$) and the number of BMs (HR, 1.01; 95% CI, 0.98-1.04; $P = .58$) were not significantly associated with an LMD diagnosis.

Treatments

Before MBM diagnosis, 199 patients (47%) had received immunotherapy, and 59 patients (14% of the total cohort; 29% of patients with BRAF mutations) had received BRAF-targeted therapy. By the time of the last follow-up, 326 patients (77%) had ever received immunotherapy, and 108 (25% of the total cohort; 52% of patients with BRAF mutations) had received BRAF-directed therapy. These treatments were not evaluated in a time-dependent manner and thus do not fully reflect the at-risk population. After a diagnosis of MBM, 39% of patients underwent surgery (craniotomy, ventriculoperitoneal shunt, or both), and 78% underwent either stereotactic radiosurgery (SRS), WBRT, or both for the treatment of MBM (Table 1; see Supporting Fig. 2). Each type of local therapy was examined as a first local/CNS treatment in relation to age, sex, year of BM diagnosis, extracranial disease, pre-BM immunotherapy, the number of BMs, dominant BM size, the presence of hemorrhage at BM diagnosis, and presenting symptoms (Table 3).

In multivariable analysis, patients who presented with headache (HR, 3.69; 95% CI, 2.05-6.64; $P < .0001$), motor/sensory deficits (HR, 1.93; 95% CI, 1.03-3.60; $P = .04$), seizure (HR, 3.23; 95% CI, 1.52-6.83; $P = .002$), or mental status change (HR, 3.65; 95% CI, 1.94-6.85; $P < .0001$) were significantly more likely to undergo craniotomy as their first treatment compared with those who presented asymptomatically. Symptomatic presentation was not significantly associated with any other treatment modality. Fewer BMs, with quantity evaluated as a continuous variable, were significantly associated with craniotomy (HR, 0.87; 95% CI, 0.81-0.93; $P \leq .0001$) and SRS (HR, 0.97; 95% CI, 0.94-1.00; $P < .04$), whereas higher BM quantity was associated the with receipt of WBRT (HR, 1.04; 95% CI, 1.03-1.06; $P < .0001$). The number of BMs was not significantly associated with receiving a shunt. Dominant BM size was significantly associated with a first treatment of craniotomy (HR, 1.38; 95% CI, 1.26-1.52; $P < .0001$) or shunt (HR, 1.72; 95% CI, 1.22-2.42; $P = .002$). For each centimeter increase in dominant BM size, patients were 72% more likely to receive a shunt and 38% more likely to undergo craniotomy. Dominant BM size was not associated with the likelihood of ultimately receiving SRS or WBRT. The presence of hemorrhage at BM diagnosis was also significantly associated with an increased likelihood of undergoing craniotomy as first treatment on multivariable analysis (HR, 1.68; 95% CI, 1.09-2.58; $P = .02$). The presence of extracranial disease was associated with a decreased likelihood of craniotomy as first treatment (HR, 0.43; 95% CI, 0.28-0.68; $P = .001$). Receipt of immunotherapy before BM diagnosis was associated with an increased likelihood of SRS as first treatment (HR, 1.74; 95% CI, 1.22-2.46; $P = .002$). Age at BM diagnosis was not significantly associated with any of the CNS-directed treatment modalities. Year of BM diagnosis demonstrated a significant association with WBRT (HR, 0.79; 95% CI, 0.73-0.86; $P < .0001$): with each subsequent year, the likelihood of receiving WBRT decreased by 21%.

Table 4 provides details of the associations of local treatment modalities, performed at any time during the disease course, with OS. In multivariable analysis, all factors that were identified as significant in univariable analysis retained significance, except for SRS. Patients who underwent craniotomy experienced improved survival compared with those who did not (HR, 0.72; 95% CI, 0.56-0.93; $P = .01$). Patients who underwent a shunt procedure (HR, 4.24; 95% CI, 2.48-7.24; $P < .0001$) and WBRT (HR, 2.65; 95% CI, 2.08-3.38; $P < .0001$) experienced shorter survival than those who did not undergo one of these treatments. Although SRS was associated with improved survival in univariable analysis (HR, 0.59; 95% CI, 0.47-0.74; $P < .0001$), it did not maintain that association when adjusted in multivariable analysis (HR, 0.87; 95% CI, 0.68-1.13; $P = .30$).

DISCUSSION

In this large, retrospective evaluation of contemporary multimodality management of patients with MBM at a large referral cancer center who were diagnosed between 2010 and 2019, we identified a progressive improvement in OS compared with historic cohorts, including controls from our own institution and even within the latter one-half of the cohort studied. The median survival was 8.9 months (95% CI, 7.6-11.2 months), and the median OS was 13.0 months among patients who were diagnosed with MBM between 2015 and 2019. The 1-year rate

TABLE 3. The Association of Variables of Interest With Specific Central Nervous System-Directed Melanoma Brain Metastasis Treatments as First Treatment

	First Treatment of Shunt								First Treatment of Craniotomy								First Treatment of SRS								First Treatment of WBRT							
			Univariable			Multivariable[a]					Univariable			Multivariable[a]					Univariable			Multivariable[a]					Univariable			Multivariable[a]		
Variable of Interest	No of Patients (%)	No. of Events (%)	Cause-Specific HR	95% CI	*P*	Cause-Specific HR	95% CI	*P*	No of Patients (%)	No. of Events (%)	Cause-Specific HR	95% CI	*P*	Cause-Specific HR	95% CI	*P*	No. of Patients (%)	No. of Events (%)	Cause-Specific HR	95% CI	*P*	Cause-Specific HR	95% CI	*P*	No. of Patients (%)	No. of Events (%)	Cause-Specific HR	95% CI	*P*	Cause-Specific HR	95% CI	*P*
No. of BM	425 (100)	10 (100)	0.73	0.48-1.09	.13				425 (100)	137 (100)	0.87	0.81-0.92	<.0001	0.87	0.81-0.93	<.0001	425 (100)	138 (100)	0.97	0.94-1.00	.03	0.97	0.94-1.00	.04	425 (100)	118 (100)	1.04	1.03-1.06	<.0001	1.04	1.03-1.06	<.0001
Dominant BM size, cm	425 (100)	10 (100)	1.71	1.32-2.20	<.0001	1.72	1.22-2.42	.002	425 (100)	137 (100)	1.57	1.46-1.70	<.0001	1.4	1.26-1.55	<.0001	425 (100)	138 (100)	0.98	0.85-1.13	.80				425 (100)	118 (100)	0.98	0.84-1.14	.78			
Age at BM Dx	425 (100)	10 (100)	0.98	0.94-1.02	.26				425 (100)	137 (100)	0.99	0.98-1.00	.24				425 (100)	138 (100)	1.00	0.99-1.01	.99				425 (100)	110 (98)	1.00	0.99-1.01	.97			
Year of BM Dx	425 (100)	10 (100)	1.19	0.89-1.60	.25				425 (100)	137 (100)	1.00	0.92-1.07	.88				425 (100)	138 (100)	1.05	0.97-1.13	.25				425 (100)	110 (92)	0.80	0.74-0.87	<.0001	0.79	0.73-0.86	<.0001
Sex																																
Female	121 (28)	1 (10)	Ref						121 (28)	38 (28)	Ref						121 (28)	40 (29)	Ref						121 (28)	39 (33)	Ref					
Male	304 (72)	9 (90)	3.42	0.43-27.04	.24				304 (72)	99 (72)	0.97	0.67-1.42	.89				304 (72)	98 (71)	0.90	0.62-1.30	.58				304 (72)	79 (67)	0.76	0.52-1.11	.16			
Hemorrhage at BM Dx																																
No	177 (42)	4 (40)	Ref						177 (42)	35 (26)	Ref			Ref			177 (42)	75 (54)	Ref						177 (42)	45 (38)	Ref			Ref		
Yes	248 (58)	6 (60)	1.36	0.38-4.87	.63				248 (58)	102 (74)	2.68	1.82-3.94	<.0001	1.68	1.09-2.58	.02	248 (58)	63 (46)	0.85	0.61-1.19	.33				248 (58)	73 (62)	1.56	1.08-2.27	.02	1.25	0.83-1.88	.29
BRAF																																
Wild type	184 (43)	2 (20)	Ref						184 (43)	56 (41)	Ref						184 (43)	72 (52)	ref			ref			184 (43)	43 (36)	ref					
Mutated	206 (48)	8 (80)	3.41	0.72-16.09	.30				206 (48)	69 (50)	1.08	0.76-1.53	.68				206 (48)	61 (44)	0.70	0.50-0.98	0.04	0.81	0.57-1.16	0.25	206 (48)	63 (53)	1.24	0.84-1.82	0.28			
Pre-BM immunotherapy																																
No	226 (53)	6 (60)	Ref						226 (53)	87 (64)	Ref			Ref			226 (53)	54 (39)	Ref			Ref			226 (53)	56 (47)	Ref					
Yes	199 (47)	4 (40)	0.77	0.22-2.74	.69				199 (47)	50 (37)	0.67	0.47-0.95	.02	0.93	0.65-1.35	.71	199 (47)	84 (61)	1.89	1.34-2.66	.0003	1.74	1.22-2.46	.002	199 (47)	62 (53)	1.31	0.91-1.88	.15			
Systemic burden at BM Dx																																
No	42 (10)	0 (0)	Ref						42 (10)	29 (22)	Ref			Ref			42 (10)	10 (7)	Ref						42 (10)	4 (3)	Ref					
Yes	372 (88)	10 (100)	No est	No est	No est				372 (88)	103 (78)	0.29	0.19-0.44	<.0001	0.43	0.28-0.68	.001	372 (88)	125 (93)	0.85	0.45-1.63	.63				372 (88)	111 (97)	2.08	0.77-5.65	.15			
Presenting symptoms																																
Asymptomatic	166 (39)	2 (20)	Ref			Ref			166 (39)	19 (14)	Ref			Ref			166 (39)	78 (57)	Ref						166 (39)	48 (41)	Ref			Ref		
Headache	72 (17)	4 (40)	8.25	1.47-46.32	.02	3.76	0.60-23.78	.16	72 (17)	41 (30)	8.06	4.66-13.93	<.0001	3.69	2.05-6.64	<.0001	72 (17)	16 (12)	0.97	0.57-1.67	.92				72 (17)	13 (11)	1.12	0.60-2.07	.73	1.17	0.63-2.18	.61
Motor/sensory	83 (20)	2 (20)	2.67	0.37-19.07	.33	0.94	0.09-9.47	.96	83 (20)	32 (23)	4.29	2.43-7.58	<.0001	1.93	1.03-3.60	.04	83 (20)	20 (14)	0.74	0.45-1.21	.23				83 (20)	29 (25)	1.60	1.01-2.54	.046	1.13	0.70-1.84	.62
Seizure	34 (8)	0 (0)	No est	No est	No est	No est	No est	No est	34 (8)	13 (9)	5.74	2.82-11.67	<.0001	3.23	1.52-6.83	.002	34 (8)	8 (6)	1.17	0.56-2.43	.67				34 (8)	11 (9)	2.17	1.12-4.20	.02	1.27	0.64-2.53	.49
Mental status change	56 (13)	2 (20)	5.17	0.71-37.76	.11	2.95	0.37-23.43	.31	56 (13)	27 (20)	6.47	3.59-11.68	<.0001	3.65	1.94-6.85	<.0001	56 (13)	11 (8)	0.74	0.39-1.40	.36				56 (13)	14 (12)	1.41	0.78-2.57	.26	1.22	0.65-2.28	.54
Other	14 (3)	0 (0)	No est	No est	No est	No est	No est	No est	14 (3)	5 (4)	3.56	1.33-9.54	.01	2.02	0.74-5.56	.17	14 (3)	5 (4)	0.89	0.36-2.20	.80				14 (3)	3 (3)	0.84	0.26-2.70	.77	1.22	0.38-3.95	.74

Abbreviations: BM, brain metastases; Dx, diagnosis; HR, hazard ratio; No est, not estimated; Ref, reference category; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
[a]Variables that were significant in the unadjusted models were brought forward.

TABLE 4. Association of Local and Central Nervous System Treatment Modalities With Overall Survival

Treatment[a]	No. of Patients (%)	Unadjusted		Adjusted	
		HR [95% CI]	*P*	HR [95% CI]	*P*
Shunt					
No	409 (96)	Ref		Ref	
Yes, time-dependent variable	16 (4)	4.14 [2.45-6.99]	<.0001	4.24 [2.48-7.24]	<.0001
Craniotomy					
No	269 (63)	Ref		Ref	
Yes, time-dependent variable	156 (37)	0.68 [0.53-0.86]	.001	0.72 [0.56-0.93]	.0099
SRS					
No	195 (46)	Ref		Ref	
Yes, time-dependent variable	230 (54)	0.59 [0.47-0.74]	<.0001	0.87 [0.68-1.13]	.3
WBRT					
No	274 (64)	Ref		Ref	
Yes, time-dependent variable	151 (36)	2.96 [2.37-3.69]	<.0001	2.65 [2.08-3.38]	<.0001

Abbreviations: HR, hazard ratio; Ref, reference category; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
[a]Treatments were analyzed as time-dependent variables, and analyses were performed at any time during the course of disease.

survival is estimated at 35.1% (95% CI, 29.1%-42.3%) for patients who were diagnosed with MBM during 2010 through 2014 and 52.4% (95% CI, 45.9%-59.8%) for those who were diagnosed between 2015 and 2019, with a median follow-up of 1.7 years for survivors of the latter group (log-rank test; $P = .0003$ across the entire survival distribution). A prior cohort of patients with melanoma at MSK from 1991 through 2001 had a median OS of 5.2 months after diagnosis of MBM.[5] Other large, historic institutional cohorts had similar survival rates of 4.1 to 4.7 months and did not reflect the current treatment environment, which has changed considerably in recent years.[4,6,7] A recent, large national database study revealed improved survival for patients who received treatment with checkpoint blockade as the first initial treatment after MBM diagnosis (12.4 vs 5.2 months), but that study was limited because the database only included patients who presented with MBM at time of initial melanoma diagnosis and did not have data on location, size, or number of BMs.[26] Our empirically identified cutoff for the most pronounced survival improvement between 2014 and 2015 coincides with the US Food and Drug Administration approval of PD-1 blockade using nivolumab and pembrolizumab as well as the subsequent approvals of combination ipilimumab plus nivolumab, dabrafenib plus trametinib, and vemurafenib plus cobimetinib. The improved 3-year survival rates in the tail of our cohort, particularly during the period from 2015 to 2019, are consistent with the increased proportion of longer term survivors conveyed by recent targeted and immunotherapy trials compared with historic cohorts.[12,15,27] This improved median survival for patients with MBM, however, remains considerably shorter than the years-long OS improvements observed among patients with advanced melanoma in general, suggesting that, although immunotherapy and targeted therapies may elicit responses in MBM, these responses may not be as frequent or durable as those in the extracranial compartments.[12,15] It remains unclear whether the increase in OS in the age of targeted therapy and immunotherapy is caused by improved systemic or CNS disease control. In an attempt to investigate this question, we classified patients as having either progressive systemic disease or CNS disease at time of death, when data were available. However, in a multivariable analysis, we did not observe any statistically significant differences in the risk of systemic or CNS progression at time of death between the years 2010 through 2014 and 2015 through 2019. Ultimately, these targeted therapy and immunotherapy agents require further investigation and the inclusion of patients with MBM in clinical trials. It is likely that these systemic modalities remain poorly efficacious relative to the CNS-penetrant strategies reported in select other BM malignancies, for example, EGFR-mutant and ALK-rearranged lung cancers.[28,29]

In addition to the changes in systemic targeted therapies, our cohort demonstrates additional developments in the treatment algorithm for BM compared with prior decades. The use of WBRT has waned because of data suggesting that WBRT, compared with SRS, causes significant cognitive decline with no significant increase in OS despite similar local and improved distant CNS control.[30-33] Currently, SRS is used increasingly for patients who have >5 BMs in light of these neurocognitive data, improving survival and given that SRS for 5 to 10 BMs was identified as noninferior to SRS treatment for those who have 2 to 4 BMs.[34] In the MSK cohort reported by Raizer and colleagues, approximately 53.5% of patients underwent WBRT compared with 21.9% who underwent SRS.[5] Our current cohort has now seen a reversal of those numbers, with 24% of patients undergoing WBRT, 43%

undergoing SRS, and 11% undergoing both; and, indeed, the year of MBM diagnosis predicted CNS radiation modality. It is possible that the increasing use of SRS in combination with immunotherapy, as observed in our cohort, could have played a role in improved survival through the hypothesized abscopal effect.[35] Coupling targeted therapies with SRS has also been shown to improve survival in a retrospective analysis.[36,37] However, the precise roles for SRS and immunotherapy remain controversial given the CNS and extra-CNS efficacy of the latter and the risk of symptomatic edema requiring corticosteroid use with the former.[38] It is possible that the increasing use of SRS contributed to the observed survival benefit after 2014; however, our institution was an early adopter of SRS for oligometastatic disease, and patients were treated with this modality before 2014. Surgery has remained a significant component in the treatment of MBM, with 37% of patients undergoing craniotomy, which is comparable to 35.5% in the cohort reported by Raizer et al. Craniotomy was used for patients who had fewer, larger, and symptomatic BMs, and its association with improved survival on multivariable analysis can be attributed both to its efficacy, in line with the established literature demonstrating survival and functional benefits for metastasectomy in both the palliative and local-control settings; and to its reservation for selected patients who are motivated to receive therapy.[39] Shunting and WBRT both were associated with a worse prognosis and OS likely because of their use as palliative, end-of-life treatments.

The factors associated with a poorer prognosis in our cohort included pre-BM immunotherapy, the number of metastases at MBM diagnosis, serum LDH level, the presence of extracranial disease burden, and LMD. These factors are consistent with prior reports.[4-7,40,41] The HR of 1.67 (95% CI, 1.07-2.59) for patients with extracranial disease in the current cohort is similar to the HR of 2.13 in our institution's previous report.[5] LMD had been identified as a poor prognostic factor in prior cohorts; however, in the current cohort, it was the strongest factor that remained statistically significant in our multivariable analysis.[5,6] The presence of ≥5 parenchymal metastases was associated with significantly worse survival in this study. This is comparable, although higher, than the previously reported 3 to 4 BM cutoff.[5,6] This increase may be related to increased evidence for and evident use of early SRS before WBRT for oligometastatic disease in the last decade.[34,42] Although other analyses have reported an association between BRAF mutation and improved survival, our cohort did not identify a similar relation. This likely can be attributed to the improved survival of patients with wild-type BRAF, who have increasingly been treated with and responding to immunotherapy.[25] Given the success of immunotherapy and *BRAF/MEK* inhibition in controlling systemic disease, and the concept of CNS privilege in particular for macromolecules, one might have expected an increase in the number of patients presenting with MBM and no evidence of extracranial disease at the time of BM diagnosis. However, the 10% rate of CNS-only disease is lower than our institution's prior report (16%) and may also reflect the reported CNS efficacy of the targeted agents, as discussed above.[5] Furthermore, treatment with immunotherapy before BM diagnosis did not significantly alter the number of BMs present at diagnosis, nor did it significantly alter the timeline of development of LMD once diagnosed with BM. However, it did portend a worse prognosis after a diagnosis of MBM, which is not surprising given that this scenario is akin to treatment failure of immunotherapy, which has more limited available salvage options.[43]

LMD remained a dismal prognostic factor in our cohort, despite the treatment advances for extracranial and CNS parenchymal control. Previous reports describe an OS of 1.2 to 4.0 months after a diagnosis of LMD, and the current cohort falls within this range, with an OS of 2.3 months after LMD diagnosis.[5,6,44] Our cohort excluded 4 patients who had a diagnosis of primary LMD, defined as LMD without parenchymal BM at MBM diagnosis. Primary LMD may represent a separate clinical entity with a particularly poor prognosis that requires separate attention and study. However, many patients are diagnosed with LMD over the course of CNS disease. Although most LMD diagnoses were made within the first 2 years after MBM diagnosis, a plateau around 3 years was observed, with approximately 15.3% of patients with MBM diagnosed with LMD at 3 years. A time-dependent analysis indicated that LMD diagnosis is a strong negative prognostic factor at any time during the course of disease. The effects of small-molecule serine-threonine kinase inhibitor therapy and immunotherapy on LMD remain poorly understood given the broad exclusion of patients who have LMD from the larger clinical trials in general. Intrathecal administration of immunotherapy has been proposed and, in the case of intrathecal IL-2, has been suggested to improve survival.[45] However, it has not been demonstrated that systemic administration of immunotherapies after an LMD diagnosis significantly benefits patients who have LMD, except in case reports.[46] Only 4 patients with LMD were treated in the combination nivolumab plus ipilimumab immunotherapy trial, with none achieving a complete response.[24] Clearly, further investigation is necessary to identify treatments that can reduce LMD development or contribute to its control.

In the current study, we assessed prognostic factors among patients who were diagnosed with MBM in the recent decade after the introduction of precision-targeted therapies and immunotherapies. Although all patients diagnosed with MBM were included, this study was not designed to assess whether immunotherapy/precision therapies decreased the rate or shifted the timeline of development of BM in patients with advanced melanoma. Whereas ipilimumab and vemurafenib were first approved by the US Food and Drug Administration in 2011, we included patients from 2010 and later because of our institution's early involvement in the clinical trials for these therapies. Given the heterogeneity of the cohort at diagnosis and its retrospective nature, this study also was not designed to compare the effectiveness of treatment paradigms. In particular, we did not specifically assess the effects of *BRAF/MEK* inhibition because of its application to only a smaller subset of patients. Furthermore, the focus of this study was to describe the treatment and prognosis of all patients with MBM. The study may be biased by its limitation to a single institution; however, is aided by the institution's early involvement in immunotherapy and targeted therapy trials for the metastatic melanoma population and a large patient population. This single-institution study also provided a unique opportunity to compare outcomes with a similarly sized cohort at the same institution from the preceding decade.[5] Going forward, however, it will be valuable to assess these prognostic factors in a validation cohort from other institutions.

Conclusions

This study demonstrates that the prognosis for patients who have MBM has improved compared with historic cohorts, and even within the later time period studied herein. The number of BMs at diagnosis, the systemic disease burden, and the presence of LMD are important prognostic indicators and can guide patient counseling. As treatment paradigms continue to evolve, both CNS-directed and systemic trials should be open to and accruing patients with MBM to understand treatment efficacy in this morbid, difficult-to-treat, and increasingly prevalent disease stage and to continue improving their prognosis.

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AUTHOR CONTRIBUTIONS

Evan D. Bander: Conceptualization, data curation, formal analysis and methodology, writing–original draft, writing–review and editing, and approved the final version. **Melissa Yuan:** Data curation and approved the final version. **Joseph A. Carnevale:** Data curation and approved the final version. **Anne S. Reiner:** Conceptualization, formal analysis and methodology, writing–original draft, writing–review and editing, and approved the final version. **Katherine S. Panageas:** Conceptualization, formal analysis and methodology, writing–review and editing, and approved the final version. **Michael A. Postow:** Formal analysis and methodology, writing–review and editing, and approved the final version. **Viviane Tabar:** Conceptualization, formal analysis and methodology, writing–review and editing, supervision, and approved the final version. **Nelson S. Moss:** Conceptualization, formal analysis and methodology, writing–original draft, writing–review and editing, supervision, and approved the final version.

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