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An integrated disease-specific graded prognostic assessment scale for melanoma: contributions of KPS, CITV, number of metastases, and BRAF mutation status

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Abstract

Background. Stereotactic radiosurgery (SRS) remains a mainstay therapy in the treatment of melanoma brain metastases (BM). While prognostic scales have been developed for melanoma patients who underwent SRS treatment for BM, the pertinence of these scales in the context of molecularly targeted therapies remains unclear.

Methods. Through a multi-institutional collaboration, we collated the survival patterns of 331 melanoma BM patients with known BRAF mutation status treated with SRS. We established a prognostic scale that was validated in an independent cohort of 174 patients. All patients with BRAF mutations in this series were treated with BRAF inhibitors. Prognostic utility was assessed using Net Reclassification Index (NRI > 0) and integrated discrimination improvement (IDI) metrics.

Results. In a multivariate Cox proportional hazards model, BRAF mutation status, KPS, number of metastases, and cumulative intracranial tumor volume (CITV) independently contributed to survival prognostication for melanoma patients with SRS-treated BM ($P < .05$ for all variables). These variables were incorporated into a prognostic scale using the disease-specific graded prognostic assessment (ds-GPA) framework. This integrated melanoma ds-GPA scale was validated in 2 independent cohorts collated through a multi-institutional collaboration. In terms of order of prognostic importance, BRAF mutation status exerted the greatest influence on survival, while KPS, the number of metastases, and CITV exhibited comparable, lesser impacts.

Conclusions. Optimal survival prognostication for SRS-treated patients with melanoma BM requires an integrated assessment of patient characteristics (KPS), tumor characteristics (CITV and number of metastases), and the mutational profile of the melanoma (BRAF mutation status).

Key Points

- BRAF status, KPS, CITV, and number of BM independently prognosticate survival.
- BRAF status most notably impacts survival, followed by CITV, KPS, and number of BM.

Importance of the Study

The success of molecularly targeted therapies has fundamentally reshaped the landscape of survivorship for patients afflicted with BRAF-mutated melanomas. However, the efficacy of these agents against brain metastases is limited. As such, SRS remains a cornerstone in the treatment of BRAF-mutated melanoma brain metastases (BM). While features of BM including total number of lesions and cumulative intracranial tumor volume (CITV), along with clinical characteristics like KPS have been shown to influence survival in melanoma patients with SRS-treated BM, limited information is available on their pertinence in the context of BRAF mutation and targeted therapy. Here, we show that BRAF mutation, CITV, number of BM, and KPS independently contribute to survival prognostication, and that optimal prognostication requires the integration of these variables. In order of prognostic importance, BRAF mutation exerted the greatest influence on survival, followed by CITV, KPS, and the number of BM exhibiting comparable, lesser impacts.

Melanoma is an aggressive malignancy with increasing world-wide incidence.[1] In general, there is a high propensity for metastasis to the central nervous system, with ~20–40% of stage IV patients suffering from brain metastases (BM).[2,3] Of known malignancies, melanoma is the third most common cause of BM, trailing only lung and breast cancer.[4] Historically, the prognosis of melanoma BM has generally been poor, with median survival ranging from 3 to 7 months.[5–7] However, recent advances in molecular targeted therapies against BRAF mutated melanomas are now extending survival past historical expectations, with median survival of BM patients going beyond a year in select series.[1,7,8] This improved clinical outcome is additionally accompanied by widened variability in observed survival.[7,8] Prognostic scales that accurately predict survival outcomes are useful in this context, to inform patient expectations as well as clinical decisions.[9,10]

While recent studies have demonstrated the efficacy of BRAF inhibitors against BM, management of melanoma BM remains largely dependent on radiation therapy or surgery.[1,11,12] Because of the intrinsic resistance of melanoma BM to radiation, conformal delivery of high dose radiation through stereotactic radiosurgery (SRS) is generally preferred in patients with limited number of metastases.[12–15] Local control of melanoma BM after SRS ranges from 63% to 90%, with poorer control as median tumor volume increases.[16–18] Despite this observation, prognostication scales for melanoma BM have yet to incorporate tumor volume as a variable.[9,19] The most updated melanoma-specific prognostic scale, termed molecularly modified graded prognostic assessment (GPA), consists of the following 5 variables: age, KPS, presence of extracranial metastases, number of metastases, and BRAF mutation status.[19]

Our previous studies demonstrated that cumulative intracranial tumor volume (CITV), defined as the sum of all BM tumor volumes, is a critical parameter that prognosticates the survival of SRS-treated BM patients for a variety of cancers.[5,20–24] There are several reasons underlying this prognostic utility. For instance, larger CITV is a reflection of increased tumor burden, which is generally associated with poor survival.[25,26] Moreover, radiation dose, a key parameter that influences local control, is largely determined by the tumor volume.[27–30] Increased local recurrence after SRS of larger BM is often attributed to radiation dose de-escalation.[30] In this context, we had previously developed a CITV-modified ds-GPA scale for melanoma and validated this scale in independent cohorts.[21] Here, we show that optimal survival prognostication requires a model that incorporates BRAF mutation status, CITV, number of brain metastases, and KPS.

Methods

Study Cohorts

All of the data were collected retrospectively and were approved by each institution's respective Institutional Review Board (IRB). The initial study cohort comprised data from the Karolinska University Hospital (treated by G.S et al.), the University of California, San Diego (treated by C.C.C.), and Yale (treated by V.C.) consisting of 331 total patients. A power calculation based on effect size from the initial study suggested that a minimum sample size of 124 patients was required for validation at a statistical power of 0.80.[31] Additional patients were collected from Cleveland Clinic (treated by M.A.), and from MD Anderson Cancer Center (treated by I.M.) to this end. A total of 173 patients were collected for this validation cohort.

All of the patients in this study bear the diagnosis of stage IV melanoma and suffered from at least one BM and were treated by single-session SRS without craniotomy as their primary medical intervention. Patients who received multiple SRS treatments were treated as new patients for each event. Patients who received immunotherapy prior to SRS were excluded in this study. The patient data were collected from in-house electronic medical records, or from the medical records of the respective institutions that provided the data. Information curated included patient KPS, number of brain metastases, overall survival (in months from last radiosurgery treatment), BRAF mutation status, and CITV. Approximately 55% of the study cohort were treated with BRAF inhibitors prior to SRS and the remaining patients underwent SRS after BRAF inhibition.

Radiosurgery Technique

Detailed descriptions of the SRS technique have previously been provided.[6,21,23] In brief, patients underwent imaging using 1mm axial and coronal slices, on T1-weighted pre- and post-contrast MRI. All patients were consulted by a multi-disciplinary team of specialists, consisting of a neurosurgeon, radiation oncologist, and medical physicist. Following MRI procedures, Elekta's Gamma Plan software was used for radiation dosimetric planning. All patients were treated with single session SRS. In all patients, the prescription dose was calculated at the 50% isodose line. Doses to the optic nerve were limited to 10 Gy, and doses to brainstem BM were limited to 18 Gy.

Statistical Analysis

Survival analysis was performed using Kaplan–Meier methods.[32] Correlative analysis of KPS, number of metastases, CITV, and BRAF mutation status was performed using Pearson's correlation.[33,34] Univariate and multivariate Cox proportional hazards regressions were performed to assess survival association. For the CITV-BRAF-modified ds-GPA model, both CITV and BRAF mutation status were dichotomized. For CITV, a cutoff of 4 cubic centimeters (cc) was used, corresponding to point values of 0 (< 4cc) and 2 (>= 4cc) as previously published.[21] For BRAF mutation status, 0 points were assigned for absence of the mutation, and 2 points for presence of the mutation. We constructed 3 different ds-GPA models (original ds-GPA, CITV-modified ds-GPA, and CITV-BRAF-modified ds-GPA) and compared them using the Akaike Information Criterion (AIC).[9,21,35] AIC is a statistical measure that compares the quality of different models by balancing goodness-of-fit with the complexity of the model, with a smaller AIC indicating a more optimal model.

Net Reclassification Index (NRI > 0) and Integrated Discrimination Improvement (IDI) were used to compare the prognostic utilities of CITV-modified ds-GPA and CITV-BRAF-modified ds-GPA.[36] In the context of this study, NRI > 0 compares prognostic models by calculating the proportion of patients who died before a year who were assigned a higher likelihood of death and the portion of patients who survive beyond a year who were assigned a higher survival likelihood. IDI measures the improvement of the average sensitivity of the new model compared with the previous model. In both cases, positive values indicate improved classification.

All statistical analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing), and the predictABEL package for NRI and IDI calculations. All tests performed were 2-tailed, with a *P*-value of <.05 required for significance.

Results

Patient and Tumor Characteristics

Patient demographics of the initial study cohort are provided in Table 1 and are largely consistent with the published literature.[1] The cohort consisted of ~50% male and female subjects. The mean age of SRS treatment was ~ 60 (standard deviation of ~15). The median KPS was 90 (interquartile [IQR] range 80–100). The median CITV was 3.11 cc (IQR 0.9–10.1), median number of BM was 2 (IQR 1–4), and median overall survival was 8.3 months (IQR 3.7–16.8). Approximately 45.9% of the melanoma patients were BRAF mutated, which is generally reflective of the incidence of BRAF mutation in metastatic melanoma.[37]

Table 1. Patient Demographics and Tumor Characteristics of the Study Cohort

Total, *N*	331
Sex (%)	
Female	170 (51.4)
Male	161 (48.6)
Age, Mean (SD)	60.69 (15.10)
KPS, Median [IQR]	90.00 [80.00, 100.00]
CITV, Median [IQR]	3.11 [0.90, 10.14]
Number of Lesions, Median [IQR]	2.00 [1.00, 4.00]
Survival In Months, Median [IQR]	8.30 [3.73, 16.77]
Survival < 12 months, *N* (%)	214 (64.7)
BRAF mutation present, *N* (%)	152 (45.9)

CITV, cumulative intracranial tumor volume; IQR, interquartile range.

Univariate Cox Proportional Hazards Analysis

In the univariate Cox proportional hazards model, we found that KPS, number of metastases, CITV, and BRAF mutation status were each associated with patient survival (Supplementary Table 1). The strongest survival association was observed with BRAF mutation status, with BRAF mutation conferring an ~26% reduction in hazard of death ($P < .001$). Number of BM, CITV, and KPS are each associated with a 3–5% change in the hazard of death ($P < .001$ for all 3 variables). Supporting the importance of BRAF mutation status in survival prognostication, Kaplan–Meier analysis independently confirmed differential survival between patients afflicted with BRAF mutated and wild-type melanoma BM (Supplementary Figure 1). Median survival of patients with BRAF wild-type and mutated melanoma BM were 6.8 and 13.2 months, respectively ($P = .002$).

We next assessed the relationships between BRAF status, number of BM, CITV, and KPS using Pearson's correlation analysis. While significant associations were observed between number of BM, CITV, and KPS, these variables were poorly correlated with BRAF mutation status (Supplementary Table 2). Importantly, BRAF mutation status was significantly associated with only number of metastatic lesions ($r = 0.13$, $P = .07$).

Multivariate Cox proportional hazards analysis

We next incorporated BRAF status, number of BM, CITV, and KPS into a single multivariate Cox proportional

hazards model (Table 2). In this model, all 4 variables were independently associated with overall survival. Of the 4 variables, BRAF status remained most potently associated with overall survival, with BRAF mutation conferring an ~28% reduction in hazard of death ($P < .001$). Number of BM, CITV, and KPS were also each independently associated with survival, exhibiting a 2–5% change in the hazard of death ($P = .043, < .001, < .001$, respectively).

Integration of Variables Into ds-GPA for Melanoma

To test the prognostic contributions of CITV and BRAF in the context of melanoma ds-GPA, it was necessary to convert these variables into a point-based system.[9] We previously established that the optimal prognostic cut-off of CITV for melanoma was 4cc.[21] In this context, we dichotomized CITV to < or ≥ 4cc, assigning point values of 2 and 0, respectively. Similarly, BRAF status was dichotomized, with BRAF mutation assigned 2 points, while wild-type BRAF was assigned a point value of 0 (Table 3). Kaplan–Meier analysis demonstrated a significant survival difference associated with CITV-BRAF-ds-GPA scores, with lower scores corresponding to poor prognosis and higher scores exhibiting longer survival (Figure 1).

We then proceeded to construct the multivariate Cox proportional hazards models corresponding to each of the previously described ds-GPA scales. The details of the models created are shown in Table 4. Additionally, in order to compare the goodness-of-fit of each of the models, the Akaike Information Criteria (AIC) corresponding to each point-based system was calculated (Table 4). Remarkably, with the inclusion of each additional variable, the AIC decreased despite the penalization generally associated with adding new variables to a model when calculating the AIC. As the difference between each of the models was > 2 it can be concluded that the inclusion of new variables optimized our model with statistical significance, as lower AICs correspond to better goodness-of-fit.

Next, we tested the prognostic utility of the CITV-BRAF-ds-GPA model in predicting 1-year survival relative to the CITV-modified ds-GPA model using the standard statistical metrics of NRI > 0 and IDI. The results of this analysis are shown in Table 5. Incorporation of BRAF status improved NRI > 0 by 0.294 ($P = .010$) and IDI by 0.017 ($P = .021$). We concluded that the inclusion of BRAF status into a CITV-modified ds-GPA scale significantly improved the model's prognostic utility.

Validation in an Independent Cohort

Finally, we sought to validate the findings of our study in a separate cohort of similar patients. Based on the size effects observed in the first study cohort, we estimated that a cohort size of 124 patients will be required to achieve statistical significance for validation. In this context, we established collaborative partnerships with MD Anderson and Cleveland Clinic that afforded the collation of an additional 173 patients. We performed the NRI and IDI analyses in this independent cohort of 173 patients and were able to recapitulate our findings. The results of this analysis are also shown in Table 5. Incorporation of BRAF status improved NRI > 0 by 0.648 ($P < .001$) and IDI by 0.076 ($P < .001$). These results confirmed that optimal survival prognostication in SRS-treated melanoma patients requires consideration of BRAF status, CITV, number of metastases, and KPS.

Table 2. Multivariate Cox Proportional Hazards Analysis

	Hazard Ratio	*P*-value
KPS	0.974	<.001
Number of Metastases	1.024	.043
CITV	1.027	<.001
BRAF mutation present	0.723	<.001

CITV, cumulative intracranial tumor volume.

Discussion

The development and clinical applications of molecularly targeted inhibitors have fundamentally transformed the clinical care of patients afflicted with BRAF mutated melanomas.[1] When treated with molecular targeted therapies, these patients exhibit notable improved local control of BM after SRS, quality of life, and overall survival.[1,38–41] In this context, we sought to incorporate BRAF mutation status into a prognostic model that we previously developed that included the variables of number of metastases, KPS, and CITV. In principle, if BRAF mutation closely

Table 3. Point Breakdown of ds-GPA Scales

	ds-GPA Model			CITV-ds-GPA Model			CITV-BRAF-ds-GPA Model		
	0	1	2	0	1	2	0	1	2
KPS	<70	70–80	90–100	<70	70–80	90–100	<70	70–80	90–100
Number of metastases	>3	2–3	1	>3	2–3	1	>3	2–3	1
CITV (cc)	—	—	—	≥4	—	<4	≥4	—	<4
BRAF mutation status	—	—	—	—	—	—	Not present	—	Present

CITV, cumulative intracranial tumor volume.

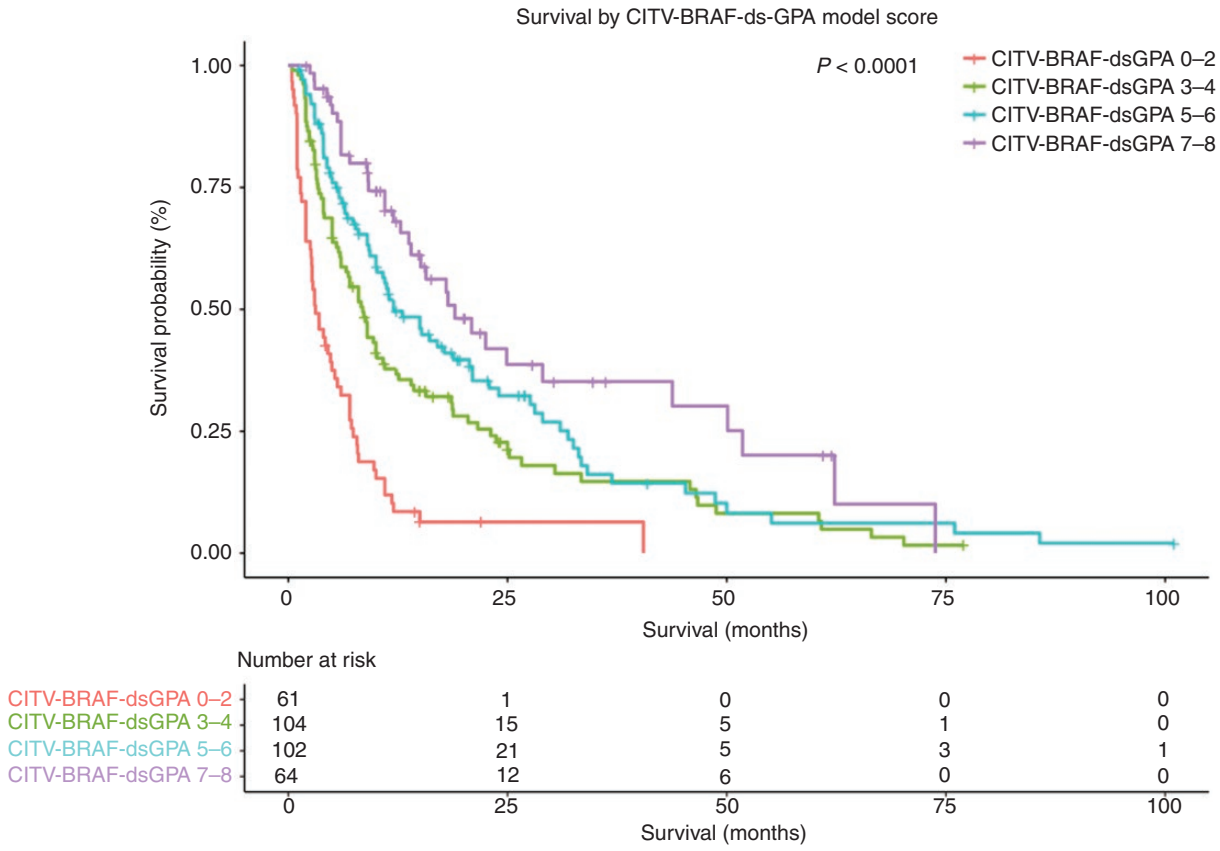

Figure 1. Kaplan–Meier survival plot of patients with different point scores using the integrated CITV-BRAF-ds-GPA model. Increasing score corresponded to significantly improved survival in our study cohort.

Table 4. Point-Based Multivariate Cox Proportional Hazards Models With AIC

	Hazard Ratio	*P*-value	Hazard Ratio	*P*-value	Hazard Ratio	*P*-value
KPS Points	0.58441	<.001	0.59063	<.001	0.59881	<.001
Number of Metastasis Points	0.67962	<.001	0.74484	<.001	0.72064	<.001
CITV Points			0.80469	.001	0.81431	.003
BRAF Points					0.85772	<.001
AIC	2,446		2,438		2,434	

AIC, Akaike Information Criteria; CITV, cumulative intracranial tumor volume.

correlated with these variables, incorporation of BRAF mutation status would likely not improve survival prognostication. For instance, if BRAF mutated melanomas always form larger BM, then CITV would capture the survival information contained within BRAF mutation status. However, the only variable that weakly correlated with BRAF mutation was the total number of brain metastases (Supplementary Table 2). Additionally, when incorporated together into a multivariate Cox proportional hazards model, each of these variables independently associated with overall patient survival. Incorporation of BRAF mutation status to our previously published CITV-modified ds-GPA model for melanoma significantly improved prognostic accuracy in a multi-institutional study cohort. Based on the effects observed in this initial cohort, we calculated the sample size required to corroborate our results and assembled a second validation cohort through collaborative partnerships. The observation that optimal prognostication required patient KPS, number of metastases, CITV, and BRAF mutation status was recapitulated in this second cohort.

To our best knowledge, this study is the first to examine the relative prognostic importance of the 4 ds-GPA variables for SRS-treated melanoma BM. In terms of order of

Table 5. Net Reclassification Improvement and Integrated Discrimination Improvement of the Study Model Incorporating BRAF Status Versus CITV-Modified Melanoma ds-GPA in the Study Cohort and Validation Cohorts

NRI and IDI Values for Study and Validation Cohorts		
	Value	*P*-value
Study cohort		
NRI	0.294	.010
IDI	0.017	.021
Validation cohort		
NRI	0.648	<.001
IDI	0.076	<.001

CITV, cumulative intracranial tumor volume; IDI, integrated discrimination improvement; NRI, Net Reclassification Index.

prognostic importance, BRAF mutation status exerted the greatest influence on survival in our study cohort, while KPS, the number of metastases, and CITV exhibited comparable, lesser impacts (Supplementary Table 1). The potency of BRAF mutation in this regard likely reflects: (1) the efficacy of BRAF inhibitors as systemic therapy for patients bearing BRAF mutated melanoma and (2) the impact of BRAF inhibitors in augmenting BM response to SRS.[1,38,39,41] In contrast, KPS, CITV, and the number of metastases mostly reflect solely the likelihood of BM response to SRS. These observations harbor implications with respect to personalizing treatment decisions for melanoma BM patients. For instance, consideration of SRS treatment for a patient with BRAF mutated melanoma, 7 BM and CITV < 4cc, fundamentally differs from that of a patient with a BRAF wild type melanoma, 7 BM and CITV > 10cc according to the scores and corresponding prognoses derived from the CITV-BRAF-ds-GPA scale for melanoma. While the proposed CITV-BRAF-modified melanoma ds-GPA scale simplifies these considerations, judicious clinical consideration beyond this scale is still required for optimal clinical decision making.

The observation that the number of melanoma BM lesions and CITV are independently associated with survival when controlling for each other in a multivariate model suggests significant heterogeneity in the volume of BM. This phenotypic heterogeneity may reflect the underlying genetic/epigenetic heterogeneity of the tumor population.[42] As clonal heterogeneity forms the basis for tumor evolution, such heterogeneity may facilitate resistance to therapeutic agents including ionizing radiation, which could explain the prognostic value of CITV.[43] However, the prognostic contribution of dose de-escalation related to SRS of BM with larger CITV cannot be discounted.[27–29] Irrespective of the biology underlying its prognostic significance, our study expands the emerging literature that highlights the importance of tumor volume as a prognostic factor for BM patients undergoing SRS as reported for distinct cancers and by independent investigators, and positions its importance in the context of molecular oncology.[5,20–24,44–48]

Our study adopts a retrospective, cross-institutional validation design, and as such is subject to limitations inherent in this type of study design, including variations in radiosurgery practices between institutions. However, the recapitulation of key results in independent cohorts despite this variation speaks to the robust nature of our conclusion. Despite this recapitulation, future prospective validation is needed to achieve scientific rigor. It is essential to additionally note that this study consisted only of patients who did not undergo surgical resection and were treated with a single session SRS. The clinical response of SRS as treatment for the postsurgical BM cavity will likely differ from the results presented here and warrant a separate study. Our study is also limited in that insufficient granularity was available to tease out the relative contributions of immunotherapy and BRAF inhibition. While patients treated with immunotherapy prior to SRS were excluded from our study to focus on the impact of BRAF inhibition, a subset of the study patients undoubtedly underwent immunotherapy treatment subsequent to SRS. As these data were not collected in our study, we were unable to singularly determine the impact of immunotherapy on the survival of our study subjects. Finally, absence of quality of life assessments in our study is problematic, particularly in the context of published data suggesting that BRAF inhibition is potentially associated with increased risk of post-SRS hemorrhage and radiation necrosis.[38,49,50] These considerations should be weighed in the context of the recently reported efficacy of BRAF inhibitors against BM.[1,11]

The rapidly changing landscape of treatment in melanoma has redefined survival expectations, challenging the value of previously established prognostic scales. While the classical ds-GPA for melanoma, a scale that has been widely accepted for the past decade, included only 2 prognostic variables, KPS and number of BM,[9] it is likely that this model requires re-evaluation in the context of molecularly targeted agents and immunotherapy. In addition to re-evaluation of clinical variables previously considered non-contributory, such as systemic disease status,[19] thoughtful characterization of the relative prognostic contribution of differing therapeutic agents, tumor genetics, as well as pharmacogenomics is warranted.[51] A truly integrated prognostic scale will require a body of work beyond that presented here in the context of a rapidly evolving treatment paradigm. The study presented here represents the first step in this process.

In summary, our study suggests that optimal prognostication in melanoma patients undergoing SRS for brain metastases requires an integrated assessment of patient characteristics (KPS), tumor characteristics (number of lesions and CITV), and the mutational profile of the cancer (BRAF mutation status). Of these variables, BRAF mutation status remains the most potent predictor of survival.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.

Keywords

brain metastasis | BRAF | CITV | ds-GPA | melanoma

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