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

Manmeet Ahluwalia, MD¹, Mir A. Ali, MD², Rushikesh S. Joshi³, Eun Suk Park, MD⁴, Birra Taha MD⁴, Ian McCutcheon, MD⁵, Veronica Chiang, MD⁶, Angela Hong MBBS, PhD⁷, Georges Sinclair, MD⁸, Jiri Bartek, Jr, MD⁸, Clark C. Chen, MD PhD⁸

¹Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland OH
²Department of Neurosurgery, Vanderbilt University Medical Center, Nashville TN
³School of Medicine, University of California San Diego, San Diego CA
⁴Department of Neurosurgery, University of Minnesota, Minneapolis MN
⁵Department of Neurosurgery, MD Anderson Cancer Center, Houston TX
⁶Department of Neurosurgery, Yale University School of Medicine, and Yale Cancer Center, New Haven, Connecticut
⁷Melanoma Institute Australia, Wollstonecraft, NSW, Australia
⁸Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden

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Corresponding author
Clark C. Chen, MD, PhD
Lyle A. French Chair of Neurosurgery
Professor and Department Head
University of Minnesota Neurosurgery

D429 Mayo Memorial Building
420 Delaware St. S.E., MMC96
Minneapolis, MN 55455
Tel: 612 626 5767
Fax: 612 624 0644
Email: ccchen@umn.edu

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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, Karnofsky Performance Score (KPS), number of metastases, and cumulative intracranial tumor volume (CITV) independently contributed to survival prognostication for melanoma patients with SRS-treated BM (p < 0.05 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 two 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).

**Keywords:** Melanoma, brain metastasis, BRAF, CITV, ds-GPA
Key Points:

1. BRAF status, KPS, CITV, and number of BM independently prognosticate survival.

2. 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 Karnofsky Performance Scale (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.
INTRODUCTION

Melanoma is an aggressive malignancy with increasing world-wide incidence. 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). Of known malignancies, melanoma is the third most common cause of BM, trailing only lung and breast cancer. Historically, the prognosis of melanoma BM has generally been poor, with median survival ranging from 3-7 months. 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. This improved clinical outcome is additionally accompanied by widened variability in observed survival. Prognostic scales that accurately predict survival outcomes are useful in this context, to inform patient expectations as well as clinical decisions.

While recent studies have demonstrated the efficacy of BRAF inhibitors against BM, management of melanoma BM remains largely dependent on radiation therapy or surgery. 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. Local control of melanoma BM after SRS ranges from 63-90%, with poorer control as median tumor volume increases. Despite this observation, prognostication scales for melanoma BM have yet to incorporate tumor volume as a variable. The most updated melanoma-specific prognostic scale, termed molecularly modified graded prognostic assessment (GPA), consists of five variables: age, Karnofsky performance status (KPS), presence of extracranial metastases, number of metastases, and BRAF mutation status.
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.\textsuperscript{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.\textsuperscript{25,26} Moreover, radiation dose, a key parameter that influences local control, is largely determined by the tumor volume.\textsuperscript{27–30} Increased local recurrence after SRS of larger BM is often attributed to radiation dose de-escalation.\textsuperscript{30} In this context, we had previously developed a CITV-modified ds-GPA scale for melanoma and validated this scale in independent cohorts.\textsuperscript{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 was collected retrospectively and was approved by each institution’s respective Institutional Review Board (IRB). The initial study cohort comprised of data from the Karolinska Institute (treated by JB), the University of California, San Diego (treated by CC), and Yale (treated by VC) 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.\textsuperscript{31} Additional patients were collected from Cleveland Clinic (treated by MA), and from MD Anderson Cancer Center (treated by IM) 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 was 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 Magnetic Resonance Imaging (MRI). All patients were consulted by a multi-disciplinary team of specialists, consisting of a neurosurgeon, radiation oncologist, and medical physicist. Following MR imaging 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.3334 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. For BRAF mutation status, 0 points were assigned for absence of the mutation, and 2 points for presence of the mutation. We constructed three 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). 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. 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, Vienna, Austria), and the predictABEL package for NRI and IDI calculations. All tests performed were two-tailed, with a p-value of p<0.05 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. 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 3.11cc (IQR
The 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.\textsuperscript{37}

**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 (Supplemental Table 1). The strongest survival association was observed with BRAF mutation status, with BRAF mutation conferring an ~26% reduction in hazard of death ($p < 0.001$). Number of BM, CITV and KPS are each associated with a 3.5% change in the hazard of death ($p < 0.001$ for all three 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 (Supplemental Figure 1). Median survival of patients with BRAF wild-type and mutated melanoma BM were 6.8 and 13.2 months, respectively ($p = 0.002$).

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 (Supplemental Table 2). Importantly, BRAF mutation status was significantly associated with only number of metastatic lesions ($r = 0.13$, $p = 0.07$).

**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 four variables were independently associated with overall survival. Of the four variables, BRAF status remained most potently associated with overall survival, with BRAF mutation conferring an ~28%
reduction in hazard of death ($p < 0.001$). Number of BM, CITV and KPS were also each independently associated with survival, exhibiting a 2-5% change in the hazard of death ($p = 0.043$, $< 0.001$, $< 0.001$, 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. We previously established that the optimal prognostic cut-off of CITV for melanoma was 4cc. In this context, we dichotomized CITV to $< 4cc$, 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 AIC’s correspond to better goodness-of-fit.

Next, we tested the prognostic utility of the CITV-BRAF-ds-GPA model in predicting one-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 \((p = 0.010)\) and IDI by 0.017 \((p = 0.021)\). 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 \((p < 0.001)\) and IDI by 0.076 \((p < 0.001)\). These results confirmed that optimal survival prognostication in SRS-treated melanoma patients requires consideration of BRAF status, CITV, number of metastases, and KPS.

**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 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 (Supplemental 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 four ds-GPA variables for SRS-treated melanoma BM. In terms of order of 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 (Supplemental 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. 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 post-surgical 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 this data was 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.\textsuperscript{38,49,50} These considerations should be weighed in the context of the recently reported efficacy of BRAF inhibitors against BM.\textsuperscript{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 two prognostic variables, KPS and number of BM\textsuperscript{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\textsuperscript{19}, thoughtful characterization of the relative prognostic contribution of differing therapeutic agents, tumor genetics, as well as pharmacogenomics is warranted\textsuperscript{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.

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REFERENCES

1. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med*. 2018;379(8):722-730. doi:10.1056/NEJMoa1805453

2. Sampson JH, Carter JH, Friedman AH, Seigler BF. Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. *J Neurosurg*. 1998;88(1):11-20. doi:10.3171/jns.1998.88.1.0011

3. Patel JK, Didolkar MS, Pickren JW, Moore RH. Metastatic pattern of malignant melanoma. A study of 216 autopsy cases. *Am J Surg*. 1978;135(6):807-810. doi:10.1016/0002-9610(78)90171-X

4. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. *Lancet*. 2004;363(9422):1665-1672. doi:10.1016/S0140-6736(04)16250-8

5. Ali MA, Hirshman BR, Wilson B, et al. Survival Patterns of 5750 Stereotactic Radiosurgery–Treated Patients with Brain Metastasis as a Function of the Number of Lesions. *World Neurosurg*. 2017;107:944-951.e1. doi:10.1016/j.wneu.2017.07.062

6. Gonda DD, Kim TE, Goetsch SJ, et al. Prognostic factors for stereotactic radiosurgery-treated patients with cerebral metastasis: Implications on randomised control trial design and inter-institutional collaboration. *Eur J Cancer*. 2014;50(6):1148-1158. doi:10.1016/j.ejca.2014.01.001

7. Sloot S, Chen YA, Zhao X, et al. Improved survival of patients with melanoma brain metastases in the era of targeted BRAF and immune checkpoint therapies. *Cancer*. 2018;124(2):297-305. doi:10.1002/cncr.30946

8. Vosoughi E, Lee JM, Miller JR, et al. Survival and clinical outcomes of patients with
melanoma brain metastasis in the era of checkpoint inhibitors and targeted therapies.

*BMC Cancer*. 2018;18(1). doi:10.1186/s12885-018-4374-x

9. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: An accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol*. 2012;30(4):419-425. doi:10.1200/JCO.2011.38.0527

10. Nieder C, Andratschke NH, Geinitz H, Grosu AL. Diagnosis-specific graded prognostic assessment score is valid in patients with brain metastases treated in routine clinical practice in two European countries. *Med Sci Monit*. 2012;18(7):CR450-CR455. doi:10.12659/MSM.883213

11. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): A multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(11):1087-1095. doi:10.1016/S1470-2045(12)70431-X

12. Chukwueke U, Batchelor T, Brastianos P. Management of brain metastases in patients with melanoma. *J Oncol Pract*. 2016;12(6):536-542. doi:10.1200/JOP.2016.011882

13. Kao WH, Riker AI, Kushwaha DS, et al. Upregulation of fanconi anemia DNA repair genes in melanoma compared with non-melanoma skin cancer. *J Invest Dermatol*. 2011;131(10):2139-2142. doi:10.1038/jid.2011.181

14. Schaue D, Mcbride WH. Opportunities and challenges of radiotherapy for treating cancer. *Nat Rev Clin Oncol*. 2015;12(9):527-540. doi:10.1038/nrclinonc.2015.120

15. Mori Y, Kondziolka D, Flickinger JC, Kirkwood JM, Agarwala S, Lunsford LD. Stereotactic radiosurgery for cerebral metastatic melanoma: Factors affecting local disease control and survival. *Int J Radiat Oncol Biol Phys*. 1998;42(3):581-589. doi:10.1016/S0360-3016(98)00272-7
16. Christ S, Mahadevan A, Floyd SR, et al. Stereotactic radiosurgery for brain metastases from malignant melanoma. *Surg Neurol Int*. 2015;6(Suppl 12):S355-S365. doi:10.4103/2152-7806.163315

17. Lippitz B, Lindquist C, Paddick I, Peterson D, O’Neill K, Beaney R. Stereotactic radiosurgery in the treatment of brain metastases: The current evidence. *Cancer Treat Rev*. 2014;40(1):48-59. doi:10.1016/j.ctrv.2013.05.002

18. Bagshaw HP, Ly D, Suneja G, Jensen RL, Shrieve DC. Local control of melanoma brain metastases treated with stereotactic radiosurgery. *J radiosurgery SBRT*. 2016;4(3):181-190. Accessed April 10, 2020. https://pubmed.ncbi.nlm.nih.gov/29296443/

19. Sperduto PW, Jiang W, Brown PD, et al. Estimating Survival in Melanoma Patients With Brain Metastases: An Update of the Graded Prognostic Assessment for Melanoma Using Molecular Markers (Melanoma-molGPA). *Int J Radiat Oncol Biol Phys*. 2017;99(4):812-816. doi:10.1016/j.ijrobp.2017.06.2454

20. Ali MAMA, Hirshman BRBR, Wilson B, et al. Improving the Prognostic Value of Disease-Specific Graded Prognostic Assessment Model for Renal Cell Carcinoma by Incorporation of Cumulative Intracranial Tumor Volume. *World Neurosurg*. 2017;108:151-156. doi:10.1016/j.wneu.2017.07.109

21. Hirshman BR, Wilson BR, Ali MA, et al. Cumulative intracranial tumor volume augments the prognostic value of the diagnosis-specific graded prognostic assessment model for survival in patients with melanoma cerebral metastases. *Clin Neurosurg*. 2018;83(2):237-244. doi:10.1093/neuros/nyx380

22. Joshi RS, Hirshman BR, Ali MA, et al. Prognostic Importance of Cumulative Intracranial Tumor Volume in Patients with Gastrointestinal Brain Metastasis Treated with Stereotactic Radiosurgery. *World Neurosurg*. 2019;121:e747-e754.
23. Marcus LP, Marshall D, Hirshman BR, et al. Cumulative Intracranial Tumor Volume (CITV) enhances the prognostic value of the lung-specific Graded Prognostic Assessment (GPA) Model. *Neurosurgery*. 2016;79(2):246-252. doi:10.1227/NEU.0000000000001123

24. Marshall DC, Marcus LP, Kim TE, et al. Management patterns of patients with cerebral metastases who underwent multiple stereotactic radiosurgeries. *J Neurooncol*. 2016;128(1):119-128. doi:10.1007/s11060-016-2084-2

25. Dickson P V., Gershenwald JE. Staging and prognosis of cutaneous melanoma. *Surg Oncol Clin N Am*. 2011;20(1):1-17. doi:10.1016/j.soc.2010.09.007

26. Oh Y, Taylor S, Bekele BN, et al. Number of metastatic sites is a strong predictor of survival in patients with nonsmall cell lung cancer with or without brain metastases. *Cancer*. 2009;115(13):2930-2938. doi:10.1002/cncr.24333

27. Rades D, Huttenlocher S, Hornung D, Blanck O, Schild SE. Radiosurgery alone versus radiosurgery plus whole-brain irradiation for very few cerebral metastases from lung cancer. *BMC Cancer*. 2014;14(1). doi:10.1186/1471-2407-14-931

28. Romano KD, Trifiletti DM, Garda A, et al. Choosing a Prescription Isodose in Stereotactic Radiosurgery for Brain Metastases: Implications for Local Control. *World Neurosurg*. 2017;98:761-767.e1. doi:10.1016/j.wneu.2016.11.038

29. Abraham C, Garsa A, Badiyan SN, et al. Internal dose escalation is associated with increased local control for non-small cell lung cancer (NSCLC) brain metastases treated with stereotactic radiosurgery (SRS). *Adv Radiat Oncol*. 2018;3(2):146-153. doi:10.1016/j.adro.2017.11.003

30. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG
protocol 90-05. Int J Radiat Oncol Biol Phys. 2000;47(2):291-298. Accessed December 31, 2017. http://www.ncbi.nlm.nih.gov/pubmed/10802351

31. Sakpal TV. Sample size estimation in clinical trial. Perspect Clin Res. 2010;1(2):67-69. Accessed September 17, 2020. http://www.ncbi.nlm.nih.gov/pubmed/21829786

32. Kishore J, Goel M, Khanna P. Understanding survival analysis: Kaplan-Meier estimate. Int J Ayurveda Res. 2010;1(4):274. doi:10.4103/0974-7788.76794

33. Gaddis ML, Gaddis GM. Introduction to biostatistics: Part 6, correlation and regression. Ann Emerg Med. 1990;19(12):1462-1468. doi:10.1016/S0196-0644(05)82622-8

34. Breslow NE. Analysis of Survival Data under the Proportional Hazards Model. Int Stat Rev / Rev Int Stat. 1975;43(1):45. doi:10.2307/1402659

35. Nagin DS, Odgers CL. Group-Based Trajectory Modeling in Clinical Research. Annu Rev Clin Psychol. 2010;6:109-138. doi:10.1146/annurev.clinpsy.121208.131413

36. Pencina MJ, D’Agostino RB, Pencina KM, Janssens ACJW, Greenland P. Interpreting Incremental Value of Markers Added to Risk Prediction Models. Am J Epidemiol. 2012;176(6):473-481. doi:10.1093/aje/kws207

37. Kong BY, Carlino MS, Menzies AM. Biology and treatment of BRAF mutant metastatic melanoma. Melanoma Manag. 2016;3(1):33-45. doi:10.2217/mmt.15.38

38. Ly D, Bagshaw HP, Anker CJ, et al. Local control after stereotactic radiosurgery for brain metastases in patients with melanoma with and without BRAF mutation and treatment. J Neurosurg. 2015;123(2):395-401. doi:10.3171/2014.9.JNS141425

39. Gallaher IS, Watanabe Y, DeFor TE, et al. BRAF mutation is associated with improved local control of melanoma brain metastases treated with Gamma Knife radiosurgery. Front Oncol. 2016;6(MAY). doi:10.3389/fonc.2016.00107

40. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data
from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol*. 2015;33(17):1889-1894. doi:10.1200/JCO.2014.56.2736

41. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med*. 2019;381(7):626-636. doi:10.1056/NEJMo1904059

42. Turajlic S, Sottoriva A, Graham T, Swanton C. Resolving genetic heterogeneity in cancer. *Nat Rev Genet*. 2019;20(7):404-416. doi:10.1038/s41576-019-0114-6

43. Mimori K, Saito T, Niida A, Miyano S. Cancer evolution and heterogeneity. *Ann Gastroenterol Surg*. 2018;2(5):332-338. doi:10.1002/ags3.12182

44. Sharma M, Jia X, Ahluwalia M, et al. Cumulative Intracranial Tumor Volume and Number of Brain Metastasis as Predictors of Developing New Lesions After Stereotactic Radiosurgery for Brain Metastasis. *World Neurosurg*. 2017;106:666-675. doi:10.1016/j.wneu.2017.07.048

45. Baschnagel AM, Meyer KD, Chen PY, et al. Tumor volume as a predictor of survival and local control in patients with brain metastases treated with Gamma Knife surgery. *J Neurosurg*. 2013;119(5):1139-1144. doi:10.3171/2013.7.JNS13431

46. Caballero JA, Sneed PK, Lamborn KR, et al. Prognostic factors for survival in patients treated with stereotactic radiosurgery for recurrent brain metastases after prior whole brain radiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;83(1):303-309. doi:10.1016/j.ijrobp.2011.06.1987

47. Likhacheva A, Pinnix CC, Parikh NR, et al. Predictors of survival in contemporary practice after initial radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys*. 2013;85(3):656-661. doi:10.1016/j.ijrobp.2012.05.047

48. Routman DM, Bian SX, Diao K, et al. The growing importance of lesion volume as a prognostic factor in patients with multiple brain metastases treated with stereotactic
radiosurgery. Cancer Med. 2018;7(3):757-764. doi:10.1002/cam4.1352

49. Xu Z, Lee CC, Ramesh A, et al. BRAF V600E mutation and BRAF kinase inhibitors in conjunction with stereotactic radiosurgery for intracranial melanoma metastases. J Neurosurg. 2017;126(3):726-734. doi:10.3171/2016.2.JNS1633

50. Colaco RJ, Martin P, Kluger HM, Yu JB, Chiang VL. Does immunotherapy increase the rate of radiation necrosis after radiosurgical treatment of brain metastases? J Neurosurg. 2016;125(1):17-23. doi:10.3171/2015.6.JNS142763

51. Sperduto PW, Jiang W, Brown PD, et al. The Prognostic Value of BRAF, C-KIT, and NRAS Mutations in Melanoma Patients With Brain Metastases. Int J Radiat Oncol Biol Phys. 2017;98(5):1069-1077. doi:10.1016/j.ijrobp.2017.03.030
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 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) |
### Table 2: Multivariate Cox proportional hazards analysis

|                                | Hazard Ratio | p-value |
|--------------------------------|--------------|---------|
| KPS                            | 0.974        | <.001   |
| Number of Metastases           | 1.024        | 0.043   |
| CITV                           | 1.027        | <.001   |
| BRAF mutation present          | 0.723        | <.001   |
Table 3: Point breakdown of ds-GPA scales

| ds-GPA model | CITV-ds-GPA model | CITV-BRAF-ds-GPA model |
|--------------|-------------------|------------------------|
| 0            | 1                 | 2                      |
| < 70         | 90-               | 70-                    |
| 70-80        | 100               | 80                     |
| KPS          |                   |                        |
| Number of    |                   |                        |
| metastases   |                   |                        |
| > 3          | 2-3               | 1                      |
| 2-3          | 1                 |                        |
| 1-3          | > 3               |                        |
| CITV (cc)    |                   |                        |
| < 4          | > 4               | < 4                    |
| > 4          | < 4               |                        |
| BRAF         |                   |                        |
| mutation     |                   |                        |
| not present  |                   | present                |
| status       |                   |                        |
| present      |                   |                        |

Table 4: Point-based multivariate Cox proportional hazards models with Akaike Information Criteria

|                      | 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      | 0.001   | 0.81431      | 0.003   |
| BRAF Points          |              |         |              |         | 0.85772      | <.001   |
| Akaike Information Criteria (AIC) |           |         | 2446         | 2438    | 2434         |         |
Table 5: Net reclassification improvement and Integrated discrimination improvement of the study model incorporating BRAF status vs. 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       | 0.010 |
| IDI       | 0.017       | 0.021 |
| **Validation Cohort** | |
| NRI       | 0.648       | <0.001 |
| IDI       | 0.076       | <0.001 |
Figure 1

Survival by CITV-BRAF-ds-GPA model score

Number at risk

| Model Score | Number at Risk |
|-------------|----------------|
| 0-2         | 61             |
| 3-4         | 104            |
| 5-6         | 102            |
| 7-8         | 64             |