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Estimating Survival in Melanoma Patients With Brain Metastases: An Update of the Graded Prognostic Assessment for Melanoma Using Molecular Markers (Melanoma-molGPA)

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Abstract

Purpose: To update the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) for a markedly heterogeneous patient population, patients with melanoma and brain metastases, using a larger, more current cohort, including molecular markers.

Methods: The original Melanoma-GPA is based on data from 483 patients whose conditions were diagnosed between 1985 and 2005. This is a multi-institutional retrospective database analysis of 823 melanoma patients with newly diagnosed brain metastases from January 1, 2006, to December 31, 2015. Multivariable analyses identified significant prognostic factors, which were weighted and included in the updated index (Melanoma-molG-PA). Multiple Cox regression was used to select and weight prognostic factors in proportion to their hazard ratios to design the updated Melanoma-molGPA in which scores of 4.0 and 0.0 are associated with the best and worst prognoses, as with all of the diagnosis-specific GPA indices. Log-rank tests were used to compare adjacent classes.

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Conflict of interest: The other authors report no conflict of interest.

Results: There were 5 significant prognostic factors for survival (age, Karnofsky performance status [KPS], extracranial metastases [ECM], number of brain metastases, and *BRAF* status), whereas only KPS and the number of brain metastases were significant in the original Melanoma-GPA. Median survival improved from 6.7 to 9.8 months between the 2 treatment eras, and the median survival times for patients with Melanoma-molGPA of 0 to 1.0, 1.5 to 2.0, 2.5 to 3.0, and 3.5 to 4.0 were 4.9, 8.3, 15.8, and 34.1 months ($P<.000l$ between each adjacent group).

Conclusions: Survival and our ability to estimate survival in melanoma patients with brain metastases has improved significantly. The updated Melanoma-molGPA, a user-friendly tool to estimate survival, will facilitate clinical decision making regarding whether and which treatment is appropriate and will also be useful for stratification of future clinical trials. To further simplify use, a free online/smart phone app is available at brainmetgpa.com.

Summary

The Graded Prognostic Assessment (GPA) is a diagnosis-specific prognostic index for patients with brain metastases. The Melanoma-GPA has been updated based on larger and more current data. Additional factors, including *BRAF* status, have been found to be prognostic. Those factors, weighted by significance, have been incorporated into the new Melanoma-molGPA. Survival and the ability to predict survival for this population has improved significantly, and the Melanoma-molGPA will facilitate clinical decision-making and stratification of clinical trials.

Introduction

Brain metastases are a common and complex conundrum for cancer care. An estimated 300,000 patients receive diagnoses each year of brain metastases in the United States (1), and that incidence is growing because of advances in treatment that result in patients living longer and thus at risk for brain metastases (2). It is a complex problem because of the marked heterogeneity of this patient population and the wide range of prior treatments (none vs extensive) they may have received at the time of diagnosis of the brain metastases. Of all malignancies, melanoma has not only the highest propensity to spread to the brain (3) but also rapidly expanding treatment options (surgery, stereotactic radiosurgery [SRS], whole brain radiation therapy [WBRT], targeted drug therapies, and immunotherapies [4]) resulting in greater heterogeneity. This heterogeneity has long plagued interpretation of clinical trials involving this patient population because it was essentially impossible to sufficiently stratify studies to verify that similar groups of patients were being compared.

This problem led to efforts to better understand prognosis, and progress was made. Gaspar et al (5) published the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis for brain metastases in 1997. This prognostic index consisted of 3 classes: class I (age <65, Karnovsky performance status [KPS] ≥70, controlled primary tumor, no extracranial metastases [ECM]), class II (all patients not in classes I or III), and class III (KPS <70), which correlated with median survival times of 7.7, 4.5 and 2.3 months, respectively.

Our group published a new more quantitative prognostic index, the Graded Prognostic Assessment (GPA) in 2008 based on age, KPS, ECM, and number of brain metastases (6).

Those prognostic factors were weighted by regression coefficients and scaled in such manner that patients with the best/worst prognosis would have a GPA of 4.0/0.0, respectively. In 2010, we refined the GPA to be diagnosis specific when we found that survival varies by diagnosis and diagnosis-specific prognostic factors (7). The Breast-GPA was then further refined using tumor subtype (8) and a summary report was published (9). More recently, the Lung-GPA was updated using molecular factors (EGFR/ALK status) (10, 11), respectively.

The original Melanoma-GPA found that only 2 factors were significant (KPS and the number of brain metastases). We recently published the effect of gene mutations on survival in melanoma patients with brain metastases (12). The purpose of this study was to update the Melanoma-GPA using molecular markers and a larger sample size from the current treatment era.

Methods

A multi-institutional retrospective institutional review board—approved database was created, comprising 823 melanoma patients with newly diagnosed brain metastases from 2006 to 2015. Variables considered included the 4 in the existing GPA: KPS, age, presence of extracranial metastases, and number of brain metastases. Additional variables included gene mutation status (*BRAF, CKIT,* and *NRAS*), sex, volume of brain metastases (for those treated with SRS), and time from primary diagnosis to brain metastases. Race was not included because of the low percentage of non white patients. Type of treatment was not considered because the purpose of a prognostic index is to estimate survival before treatment.

Statistical analyses

Multiple Cox regression was used to initially select and weight variables to be included in the new Melanoma-molGPA. The primary endpoint was overall survival measured from the start of treatment for brain metastases. Continuous variables were categorized to assess potential nonlinear effects. Both effect magnitude (hazard ratio) and statistical significance were used to select variables. Variables with larger hazard ratios were given larger point values. The final index was chosen on the basis of separation of prognostic classes with respect to overall survival, distribution of patients, and simplicity. Log-rank tests were used to compare adjacent classes.

Results

The patient characteristics, survival by gene status (*BRAF, CKIT,* and *NRAS*), risk of death by treatment and treatment era, and a summary of drug therapy for this patient cohort have been previously published (13). The treatment breakdown for the 823 patients was as follows: 56% SRS alone, 12% surgery + SRS, 11% WBRT, 9% WBRT + SRS, 4% surgery + WBRT, and 1% surgery + WBRT + SRS.

Table 1 shows the multivariable model used to select and weight factors in the Melanoma-molGPA. Five prognostic factors were found to be significant for survival in the current

study: age, KPS, extracranial metastases, number of brain metastases, and *BRAF* status, whereas only 2 (KPS and number of brain metastases) were significant in the original Melanoma-GPA study (10). The overall median survival times for patients in this cohort and the original Melanoma GPA study (1985–2005, n = 481) were 9.8 and 6.7 months ($P<.001$), respectively. Similarly, survival by GPA group also improved: Melanoma-molGPA of 0 to 1.0,1.5 to 2.0,2.5 to 3.0, and 3.5 to 4.0 were 4.9, 8.3, 15.8, and 34.1 months, respectively ($P<.0001$ between each adjacent group) compared with the prior era (GPA 0–1.0, 1.5–2.0, 2.5–3.0, and 3.5–4.0 were 3.4, 4.7, 8.8, and 13.2 months, respectively). Figure 1 shows a comparison of the Kaplan-Meier curves for the original and the new Melanoma-GPA for survival by GPA class. Both demonstrate clear separation between adjacent classes and together reflect the improvement in survival between the 2 study periods. Notably, the GPA for the worst prognostic group (GPA 0.0–1.0) has increased slightly from 3.4 to 4.9 months whereas the GPA for the best prognostic group (GPA 3.5–4.0) has improved markedly from 13.2 to 34.1 months. The distribution of patients by class shows that 17% of patients are in the worst prognostic group in both the prior and current studies, whereas 23% and 5% of patients were in the best prognostic group in the prior and current studies, respectively.

The factors analyzed and found not to be significant for survival were gender, volume of brain metastases, CKIT and NRAS status, and time from primary diagnosis to the diagnosis of brain metastases.

Table 2 shows the definition of the updated Melanoma-molGPA in a worksheet format designed to facilitate quick and easy calculation of the GPA score. To further simplify this process, a free online smartphone app has been updated and is available at brainmetgpa.com.

Discussion

A better estimate of survival will facilitate the doctor/patient/family discussion of whether and which treatment is appropriate. A patient with a Melanoma-molGPA of 3.5 to 4.0 can expect to live nearly 3 years, and more aggressive treatment may be indicated. On the other hand, a patient who has a GPA of 0.0 to 1.0 has an expected survival of <5 months and therefore may choose hospice. These decisions are difficult, and the cost of hope can be enormous (13). The QUARTZ trial, a randomized trial of dexamethasone and supportive care versus WBRT in lung cancer patients with brain metastases, showed no difference in survival or quality of life (14). Even though WBRT is now used less than in the past, a trend also reflected in the treatment patterns reported here between the 2 eras (1985–2005 and 2006–2015), the QUARTZ trial raises the question of when to treat and when to refer to hospice. This and the other updated diagnosis-specific GPA indices inform that decision (9, 11).

Whereas *BRAF*-targeted therapy and immunotherapy have clearly had an impact on outcomes in melanoma in general, it remains unresolved whether these agents benefit patients with brain metastases. In fact, our group recently published a review of the relevant literature and the possible explanations for the findings that the extracranial response to these agents exceeds the intracranial response (12).

Limitations

The study is retrospective, so despite the large sample size, there is the inherent selection bias present in all retrospective studies. Accordingly, we cannot conclude that 1 treatment is better than another. Furthermore, the type, timing, combination, and sequence of chemotherapies, targeted therapies, and immunotherapies, both before and after the diagnosis of brain metastases, varied widely, thus precluding any conclusion regarding the efficacy of those agents. Another limitation is the percentage of patients with unknown mutation status (29% *BRAF,* 65% *NRAS,* 64% *CKIT*), which is mostly due to the timing within our study period that these tests were initiated at the various centers.

In conclusion, this updated prognostic index, the Melanoma-Graded Prognostic Assessment (Melanoma-molGPA) incorporates molecular markers and provides a user-friendly tool to estimate survival for melanoma patients with brain metastases and is useful in clinical decision making and stratification of future clinical trials. Accurate stratification is crucial to interpretation of the results of clinical trials in this markedly heterogeneous patient population.

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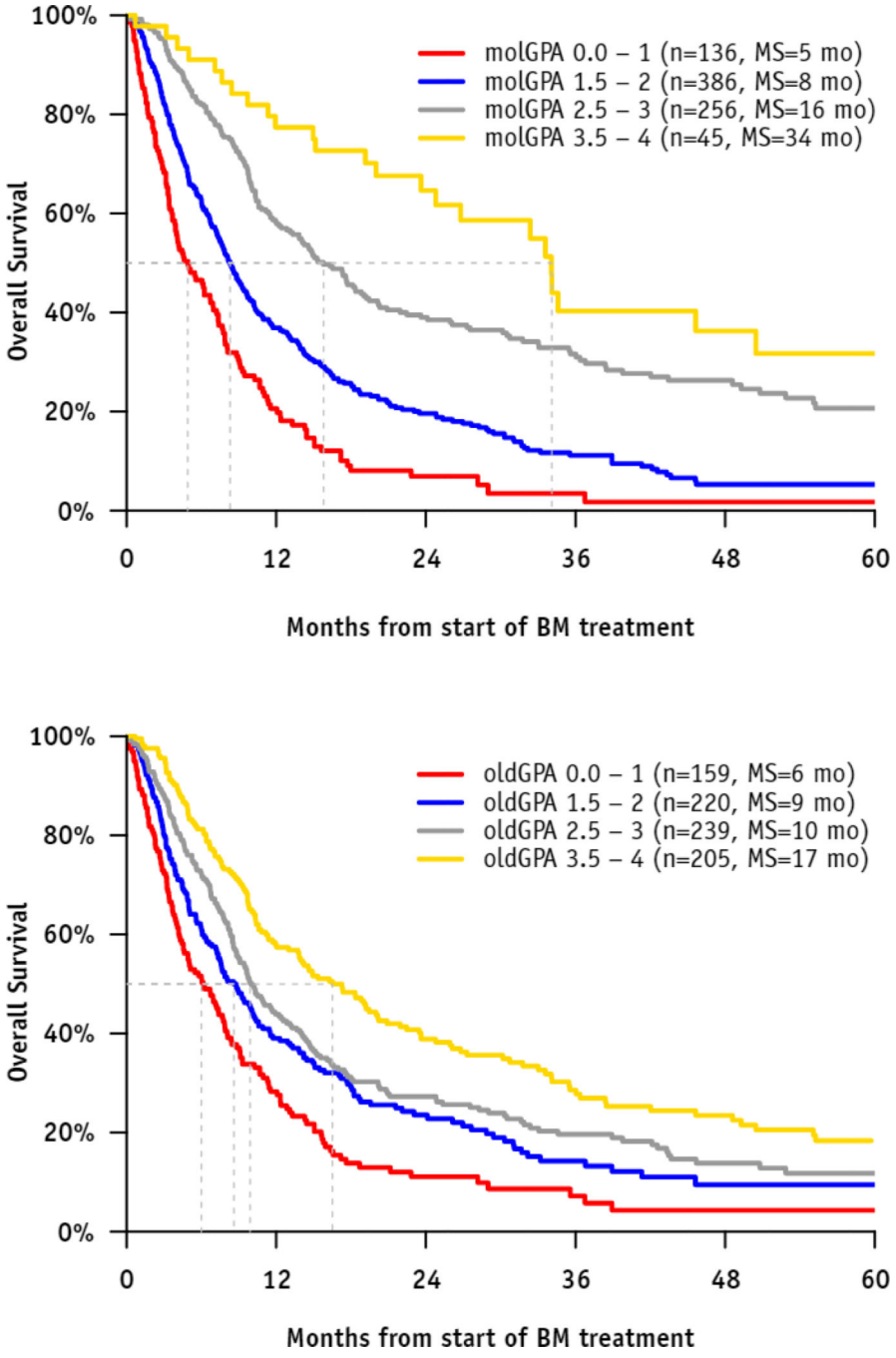

Fig. 1.

Kaplan-Meier curves comparing the original and new melanoma-GPA. *Abbreviations:* BM = brain metastases; GPA = Graded Prognostic Assessment; MS = median survival in months.

Table 1

Hazard ratios of significant prognostic factors used to derive melanoma-GPA

Variable	n	Hazard ratio	95% Confidence interval
Age, y			
<70	651	1.00	
70–97	172	1.41	1.16–1.71
KPS			
60–70	178	2.24	1.77–2.83
80	192	1.34	1.09–1.64
90–100	453	1.00	
ECM			
Absent	136	1.00	
Present	687	2.06	1.61–2.65
No. of BM			
1	328	1.00	
2–4	303	1.27	1.05–1.55
>4	192	1.72	1.38–2.14
BRAF status			
Positive	297	1.00	
Negative	287	1.30	1.06–1.58
Unknown	239	1.94	1.52–2.48

Abbreviations: BM = brain metastases; ECM = extracranial metastases; GPA = Graded Prognostic Assessment; KPS = Karnofsky performance status.

A multiple Cox regression model for overall survival from start of BM treatment is shown, with hazard ratios of 1.0 representing the reference group of each variable.

Table 2

Melanoma GPA worksheet

Prognostic factor	GPA scoring criteria			Patient Score
	0	0.5	1.0	
Age, y	≥70	<0		-
KPS	≤70	80	90–100	-
ECM	Present		Absent	-
No. of BM	>4	2–4	1	-
BRAF gene status	Negative/unknown	Positive		-
			Sum	-

Abbreviations: BM = brain metastases; ECM = extracranial metastases; GPA = Graded Prognostic Assessment; KPS = Karnofsky performance status; MS = median survival in months.

MS by GPA: 0–1.0 = 4.9, 1.5–2.0 = 8.3, 2.5–3.0 = 15.8, 3.5–4.0 = 34.1.