Original Article

Can current prognostic scores reliably guide treatment decisions in patients with brain metastases from malignant melanoma?

ABSTRACT

Purpose: We evaluated the performance of the new 4-tiered melanoma-specific graded prognostic assessment (GPA) score and the previously published general GPA score in patients with brain metastases from malignant melanoma managed with different approaches including best supportive care.

Materials and Methods: Retrospective analysis of 51 patients. Compared with the original analysis of the melanoma-specific GPA score, these patients were more representative of the general population of patients with brain metastases from this disease.

Results: The present data confirmed that both scores identify patients with favorable prognosis who might be candidates for focal treatments. However, survival in the 2 unfavorable prognostic subgroups defined by the melanoma-specific GPA was not significantly different. Median survival in the melanoma-specific GPA classes was 3.1, 3.7, 7.5, and 12.7 months. Karnofsky performance status (KPS) and serum lactatdehydrogenase (LDH) level significantly predicted survival.

Conclusion: In order to select the right patient to the right treatment and avoid overtreatment and suboptimal resource utilization in patients with very limited survival, improved prognostic tools are needed. The melanoma-specific GPA does not include extracranial disease extent or surrogate markers such as LDH. We suggest that a combination of KPS <70 and elevated LDH might better predict short survival than any of the GPA scores. This hypothesis should be confirmed in larger studies.

KEY WORDS: Best supportive care, brain metastases, malignant melanoma, radiotherapy

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INTRODUCTION

Development of brain metastases continues to be an important problem in the management of patients with advanced stages of malignant melanoma and median survival is approximately 4 to 5 months.[1,2] Treatment options include corticosteroids and supportive measures, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), surgical resection, and combinations thereof. Avoiding overtreatment in patients with poor prognosis is crucial when trying to avoid unnecessary complications and achieve maximum value for healthcare budget. The challenge is to assign the right patient to the right treatment, with clear objectives set up front, e.g., palliation of symptoms in the terminal phase of disease. Robust and reproducible prognostic models might guide clinical decision making. However, there has been no generally accepted prognostic score for patients with brain metastases from malignant melanoma. Sperduto *et al.* have recently published an analysis that expands their initial work where they evaluated data from five randomized Radiation Therapy Oncology Group (RTOG) trials on treatment of brain metastases.[3] They had initially arrived at a score that was named Graded Prognostic Assessment (GPA).[4] In the GPA system, three different values (0, 0.5, or 1) were assigned for each of these four parameters: age (≥60; 50-59; <50), Karnofsky performance status (KPS, <70; 70-80; 90-100), number of brain metastases (>3; 2-3; 1), and extracranial metastases (present; not applicable; none). The patients with the best prognosis would have a GPA of 4.0. Sperduto *et al.* have extended their work by creating diagnosis-specific GPA scores, e.g., for patients with primary malignant melanoma.[3] In the latter group, which included 483 patients, only 2 factors were significantly associated with survival, KPS, and number of brain metastases. Sperduto *et al.* assigned two points for KPS 90-100 and single brain metastasis. One point was assigned for KPS 70-80 and 2-3 brain metastases. Also, in this scoring system, the patients with the best prognosis would have a GPA of 4.0. A drawback of this analysis is that it included selected patients, 76% of whom had SRS as a component of their treatment. Most practicing oncologists will be faced with a more general patient population where a proportion of patients will be managed with best

supportive care (BSC). It is therefore important to validate the melanoma-specific GPA in such populations and examine its ability to select patients who safely can be managed with BSC. The present analysis addresses these issues.

MATERIALS AND METHODS

We analyzed patients from a previously described multi-institutional brain metastases database, which is maintained and updated at the first author's institution.[5,6] The patients were treated at three different institutions in Germany and Norway. For this retrospective study, all patients with primary malignant melanoma treated between January 1990 and March 2010 were selected (n = 51). Nine patients were alive at last follow-up (June 15, 2010), with a median follow-up of 6 months (range, 3.5-62). The patient characteristics are shown in Table 1. The prognostic impact of all these parameters was tested in univariate analyses (log-rank test). All patients were assigned to the general and diagnosis-specific GPA. Elevated serum lactatdehydrogenase (LDH) was defined as ≥205 U/l. For comparison of dichotomous variables, the Chi Square Test and Fisher's Exact Test, where applicable, were employed and for continuous variables, the Mann-Whitney *U* Test. Actuarial survival was calculated with the Kaplan-Meier method and compared between different groups with the log-rank test. For multivariate analysis of survival, Cox regression analysis was used. A *P* value ≤0.05 was considered statistically significant.

RESULTS

Treatment was individualized taking into account number of brain metastases, surgical accessibility, and several prognostic factors, but without applying a prognostic score. Five patients (10%) were managed with BSC. The reasons for withholding radiotherapy were extracranial metastases plus KPS <70 in 4 cases and extracranial metastases plus age >80 years in 1 case. Thirty patients (59%) were managed with WBRT alone. The fractionation schedule was at the discretion of the treating radiation oncologist. The different WBRT regimens administered are shown in Table 2. The remaining 16 patients received some type of focal treatment, e.g., SRS or surgery with or without WBRT. Figure 1 displays the actuarial survival curves for patients managed with BSC, primary WBRT, and surgery or SRS. Median survival was 0.7 months in the BSC group, 3.1 months in the WBRT group, and 7.5 months in the surgery/SRS group.

The most important prognostic factor was KPS. Median survival was 15.1 months in patients with KPS 90-100, 4.6 months in those with KPS 70-80, and 2.0 months in those with KPS <70 ($P = 0.01$). The second most important prognostic factor was LDH. Median survival was 6.3 months in patients with normal LDH and 3.0 months in patients with elevated LDH ($P = 0.05$). All other parameters tested were not statistically significant [Table 3]. However, patients without extracranial metastases had numerically longer median survival (9.4 months) than patients with extracranial metastases (3.2 months). Patients whose extracranial disease extent was classified as M1c had median survival comparable with M1a or M1b. Patients with solitary brain metastasis had numerically longer median survival (5.9 months) than those with 2-3 brain metastases (3.7 months) or more than 3 brain metastases (3.1 months). Multivariate analysis revealed important interactions between KPS and LDH. For example, the majority of patients with KPS 90-100 had normal LDH, whereas the majority of patients with KPS <70 had elevated LDH. Thus, KPS was the only independent prognostic factor.

Median survival stratified by general GPA score was 2.3 months (0-1 points), 6.3 months (1.5-2.5 points), and 10.9 months (because of the low number of cases, the 2 groups with 3 and 3.5-4 points were combined) [Figure 2], $P = 0.04$. The melanoma-specific GPA score did not fully discriminate between the 2 unfavorable groups. Median survival was 3.1 months (0-1 points), 3.7 months (2 points), 7.5 months (3 points), and 12.7 months (4 points) [Figure 3], not statistically

Table 1: Pretreatment characteristics of all 51 patients included in this study

Parameter		
Median Karnofsky performance status	70 % (range 40-100)	
Median age	57 years (range 24-93)	
Median interval from primary cancer diagnosis to brain metastases	18 months (range 0-125)	
Median number of brain metastases	3 (range 1-25)	
Median size of the largest brain metastasis	2.8 cm (range 0.8-7.0)	
	Number	**Percent**
Sex: female, male	24, 27	47, 53
Number of brain metastases: 1, 2-3, more than 3	12, 15, 24	24, 29, 47
Primary tumor: controlled, uncontrolled	44, 7	86, 14
Serum lactatdehydrogenase (LDH): elevated, normal, unknown	17, 16, 18	33, 31, 35
Extracranial metastases: absent, present, unknown	10, 41, 0	20, 80, 0
Extracranial stage M1a (soft tissue/ lymph node metastases, normal LDH)	3	6*
M1b (lung metastases, normal LDH)	5	11*
M1c (others)	29	62*

*missing data in 4 patients (8%)

Table 2: Treatment administered in all 51 patients included in this study

Treatment	Number (%)
Best supportive care	5 (10)
Neurosurgery*	11 (22)
Any radiosurgery**	5 (10)
Only WBRT, 4 fractions of 5 Gy	3 (6)
Only WBRT, 10 fractions of 3 Gy	19 (37)
Only WBRT, 36-39 Gy total dose	8 (16)
WBRT 30 Gy + local boost	2 (4)
Systemic chemotherapy after treatment for brain metastases	6 (12)

WBRT: whole-brain radiotherapy, *Includes 6 patients who received immediate postoperative WBRT and 3 who received salvage WBRT, **Includes 2 patients with upfront WBRT and 3 with planned WBRT after radiosurgery

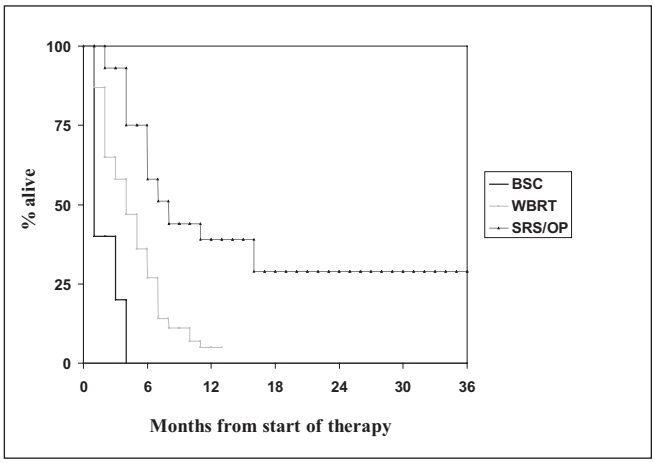

Figure 1: Kaplan-Meier curves for overall survival: best supportive care (BSC, n = 5) *vs* whole-brain radiotherapy (WBRT, n = 30) *vs* stereotactic radiosurgery (SRS) and surgery (OP, n = 16), *P* = 0.02

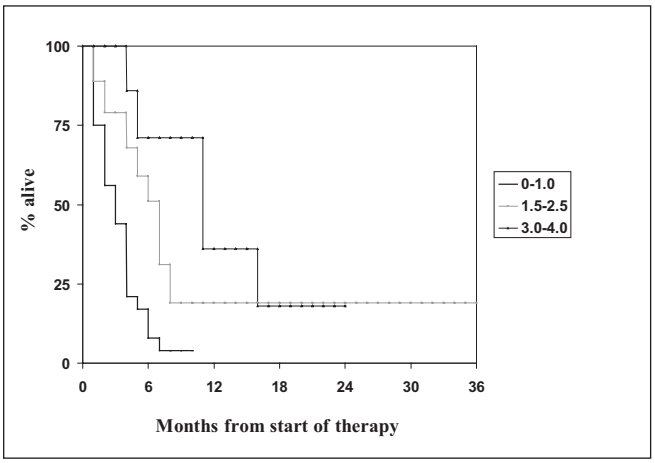

Figure 2: Kaplan-Meier curves for overall survival: general graded prognostic assessment (GPA) score 0-1 points (n = 25) *vs* 1.5-2.5 points (n = 19) *vs* 3-4 points (n = 7), *P* = 0.04

Table 3: Analyses of prognostic factors for survival

Parameter	Median survival (months)	Hazard ratio	Univariate *P*-value	Multivariate *P*-value
Karnofsky performance status 90-100	15.1	Reference group		
Karnofsky performance status 70-80	4.6	3.2	0.01	0.02
Karnofsky performance status <70	2.0	7.5		
Age <57 years	4.0	Reference group	0.4	Not included
Age ≥57 years	3.1	1.3		
Interval 0 months	5.8	Reference group		
Interval 1-18 months	4.0	1.4	0.2	Not included
Interval >18 months	3.0	1.9		
Single brain metastasis	5.9	Reference group		
2-3 brain metastases	3.7	1.6	0.35	Not included
>3 brain metastases	3.1	1.9		
Largest brain metastasis <2.8 cm	3.7	Reference group	0.8	Not included
Largest brain metastasis ≥2.8 cm	3.5	1.1		
Female patients	3.8	Reference group	0.5	Not included
Male patients	3.3	1.2		
Controlled primary tumour	3.9	Reference group	0.3	Not included
Uncontrolled primary tumour	3.0	1.3		
Normal serum lactatdehydrogenase	6.3	Reference group	0.05	0.1
Elevated serum lactatdehydrogenase	3.0	2.1		
Extracranial metastases absent	9.4	Reference group	0.09	Not included
Extracranial metastases present	3.2	2.9		
Extracranial stage M1a	3.5	Reference group		
Extracranial stage M1b	5.9	0.6	0.85	Not included
Extracranial stage M1c	3.0	1.2		

significant. Would it be prudent to withhold radiotherapy in patients assigned to the most unfavorable GPA group, i.e., 0-1 points? Regarding the melanoma-specific GPA score, 23 patients belonged to the most unfavorable group. Three were managed with BSC and survived for less than 4 months. The other 20 patients received WBRT or even surgical treatment (n = 3). Of these 20 patients, 7 survived for at least 4 months. Overall, 7 of 23 patients (30%) survived for at least 4 months. Regarding the general GPA score, 25 patients belonged to the most unfavorable group. Five were managed with BSC and survived for less than 4 months. The other 20 patients received WBRT or even SRS or surgical resection (n = 2). Of these 20 patients, 5 survived for at least 4 months. Overall, 5 of 25 patients (20%) survived for at least 4 months. In an exploratory analysis, the 2 most important prognostic factors identified in our patients were used, i.e., KPS <70 and elevated LDH. This analysis was restricted to 33 patients with available LDH. Seven patients had both KPS <70 and elevated LDH. Four patients were managed with BSC and survived for less than 4 months. The other 3 patients received WBRT. Their survival was also less than 4 months. When restricting the analysis of general and melanoma-specific GPA to the same 33 patients, the survival rates beyond 4 months changed marginally (22 instead of 20%, 33% instead of 30%). Thus, restricting the analysis to 33 patients did not explain the numerically better performance of the KPS/LDH combination model. Statistical

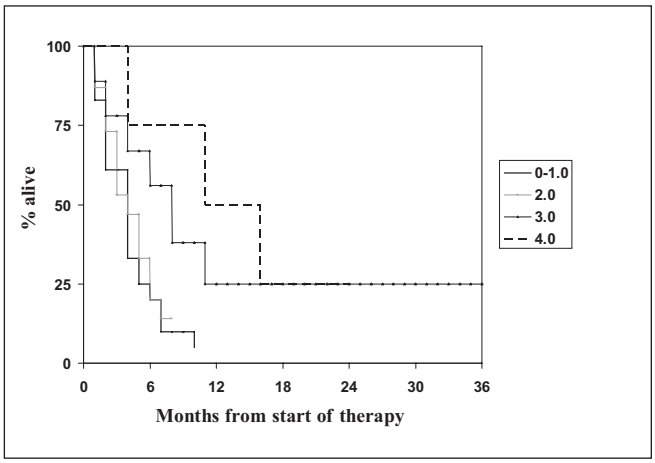

Figure 3: Kaplan-Meier curves for overall survival: melanoma-specific graded prognostic assessment (GPA) score 0-1 points (n = 23) *vs* 2 points (n = 15) *vs* 3 points (n = 9) *vs* 4 points (n = 4), $P = 0.28$

significance was not achieved in this small group of patients.

DISCUSSION

A variety of prognostic scores for patients with brain metastases from different primary tumors have been published (reviewed in).[7] The 3-tiered RTOG recursive partitioning analysis score, which also has been evaluated in studies of malignant melanoma brain metastases,[8,9] has been replaced by the 4-tiered GPA score.[4] Recently, a need for diagnosis-specific (or primary tumor-specific) scores has been identified. It has been suggested that the melanoma-specific GPA might be clinically useful.[3] The latter score was developed in a multi-institutional analysis of 483 patients treated with different approaches between 1985 and 2007. Median survival was 2.9 months after WBRT (3.1 months in the present study, 3.4 months in the study by Fife *et al.*,[2] 2.3 months in the study by Buchsbaum *et al.*).[8] Longer survival after SRS and/or surgery with or without WBRT has been reported in the melanoma-specific GPA study as well as different other retrospective studies,[2,8,10-12] the present one, and several analyses of SRS.[13-15] Evidence from melanoma-specific prospective randomized trials is not available but it has become common practice to offer SRS or surgery to selected patients with favorable prognostic features. Importantly, not all patients are candidates for aggressive local treatment. As the choice of treatment is challenging, development of tools that might guide clinicians is of great importance. This is, to the authors' best knowledge, the first analysis that attempts to validate the melanoma-specific GPA. Moreover, it extends the results to a broader group of patients including those managed with BSC. The median KPS in our patients was 70, as compared with 90 in the patients analyzed by Sperduto *et al.*[3] Therefore, the present analysis is likely more representative of unselected patient populations served by many oncology practitioners or community hospitals. As shown in Table 4, the melanoma-specific GPA predicts survival in a relatively reproducible manner. Both general and melanoma-specific GPA identify patients with favorable prognosis [Figures 2 and 3], which might be suitable for SRS or surgery.

It is equally important but more challenging to predict which patients might best be served with BSC. Patients managed with BSC had short survival in the present study and the one by Buchsbaum *et al.* (median, 1.1; range, 0.1-3.0 months).[8] A large Australian series included 327 patients managed with BSC between 1952 and 1984 and another 210 patients from the era 1985-2000.[2] Median survival was 1.7 months (range, 0.8-3.4) in patients treated in the earlier part of the study and 2.1 months (range, 0.9-5.0) in those treated after 1984. During the time period 1996-2000, 26% of patients were managed with BSC. In contrast, only 10% of our patients were managed with BSC despite survival <2 months in 15 of 51 patients (29%). These data suggest that overtreatment and suboptimal resource utilization are issues that need to be addressed. In fact, the Australian data showed a hazard ratio of 0.85 (95% confidence interval, 0.7-1.04; $P = 0.11$) for the survival comparison between radiotherapy alone *vs* BSC (1985-2000; 210 and 236 patients, respectively). These data justify a prospective randomized comparison between palliative WBRT and BSC in melanoma patients with adverse prognostic features who are not candidates for focal treatments such as SRS or surgery. The analysis of prognostic factors in the Australian study was hampered by a lack of information on performance status. Of the parameters included, presence of extracranial metastases was most important. This finding is in contrast to the melanoma-specific GPA, which does only include KPS and number of brain metastases, but was derived from a predominantly SRS-treated patient group. Importantly, several other large studies found that extracranial disease extent is an important prognostic factor,[16-18] underlining the problem with patient selection in the diagnosis-specific GPA study. Our own data question the superiority of melanoma-specific over general GPA in an unselected patient population where those managed with BSC are included. However, it is possible that the lack of significant survival differences between the 2 unfavorable groups in the melanoma-specific GPA analysis might result from limited statistical power of the relatively small sample size in this study. In other words, the present study was not adequately powered to detect the

Table 4: Comparison of the median survival results with those reported by Sperduto *et al.*[3] (number of patients in each group not reported in[3])

Study	n	All patients	DS-GPA 0-1	DS-GPA 2	DS-GPA 3	DS-GPA 4
Sperduto *et al.*	483	6.7	3.4	4.7	8.8	13.2
Present study	51	3.7	3.1 (n = 23)	3.7 (n = 15)	7.5 (n = 9)	12.7 (n = 4)

DS-GPA: diagnosis-specific graded prognostic assessment score (in this case limited to patients with malignant melanoma)

difference observed by Sperduto *et al.* (3.4 *vs* 4.7 months or +38%). A *post hoc* analysis showed a statistical power of approximately 62% (α error level 5%, one-tailed test). With 23 and 15 patients in these 2 groups, our study was powered to detect a 60% increase in median survival. The results also demonstrate that none of the GPA scores can replace clinical judgment when a decision pro or contra BSC has to be made because 30% of patients in the most unfavorable melanoma-specific GPA group survived for at least 4 months (20% when using the general GPA). We suggest that a combination of KPS <70 and elevated LDH might be less error-prone, but this finding resulted from a subgroup analysis, was not statistically significant, and has to be interpreted with caution. The survival cut-off of 4 months was arbitrarily chosen and is no generally accepted limit. It corresponds to the median survival in the large Australian study,[2] which also showed that very few patients managed with BSC experienced longer survival.

In general, the number of patients in our study was limited and so was the statistical power. Another drawback is the lack of information on LDH in 35% of the patients. LDH has only been included in one previous analysis that confirmed its independent prognostic impact in a series of 265 patients,[12] but was not available in the diagnosis-specific GPA study by Sperduto *et al.* Its potential importance is also reflected by the present, though preliminary results and the fact that it influences the malignant melanoma staging system (M1a and M1b requires normal LDH). It appears justified to evaluate the prognostic impact of LDH in patients with brain metastases in additional large studies. Both GPA scores represent progress over previous models. However, uncritical use of the existing prognostic scores should be avoided.

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