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Diagnosis-specific graded prognostic assessment score is valid in patients with brain metastases treated in routine clinical practice in two European countries

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Assessment of cancer- and host-related prognostic factors has a long tradition in patients with brain metastases. In continuation of large-scale studies performed by the Radiation Therapy Oncology Group (RTOG) in the United States, the 4-tiered diagnosis-specific graded prognostic assessment (DS-GPA) score has been developed. It stratifies patients with common primary tumours metastasizing to the brain (malignant melanoma, lung, breast, kidney and gastrointestinal cancers) into subgroups with different prognoses. However, many patients in the DS-GPA study were treated with surgical resection or radiosurgery (SRS). The present multi-institutional analysis examined for the first time whether DS-GPA is a valid score in European patients managed in routine clinical practice.

Material/Methods: This was a retrospective analysis of 412 patients with primary malignant melanoma, lung, breast, kidney or gastrointestinal cancers. Survival was evaluated in uni- and multivariate tests.

Results: DS-GPA significantly predicted survival and outperformed initial GPA, a score that is not diagnosis-specific. Median survival by DS-GPA strata (all 412 patients) was 2.7, 3.6, 7.0 and 11.3 months in the 4 groups with 0–1, 1.5–2, 2.5-3 and 3.5–4 points, respectively. The previously published survival data (median 7.2 months for all patients) could not be replicated in this cohort (median 3.6 months).

Conclusions: DS-GPA is a valid prognostic score that might improve shared decision making as well as patient stratification in prospective clinical trials.

key words: **brain metastases • radiotherapy • radiosurgery • prognosis • prognostic score**

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Background

The 4-tiered diagnosis-specific graded prognostic assessment (DS-GPA) score is the most recent brain metastases survival prediction model [1]. It is considered to represent an important evolution and refinement of the initial GPA score [2] and is expected to become widely adopted, comparable to the Radiation Therapy Oncology Group (RTOG)'s recursive partitioning analysis (RPA) score, which was published in 1997 [3]. Disease-specific aspects related to metastatic breast cancer, malignant melanoma, renal cell carcinoma, gastrointestinal cancers and lung cancers have been taken into account (scoring principles are shown in Table 1), while the initial GPA score was not stratified by primary tumour type. Very likely, typical patient populations that many oncologists in Europe will face in everyday practice are different from those included in the multi-institutional database (11 institutions from the United States and Canada, time period 1985 to 2007), which was analyzed to create the DS-GPA. For example, more than 50% of patients in each diagnosis stratum had surgery or radiosurgery (SRS) as a component of treatment, except for those with small-cell lung cancer (whole-brain radiotherapy [WBRT] in 81%). It is therefore important to validate this score in European patients and to confirm its advantages over older 4-tiered scores such as GPA [2] and Basic Score for Brain Metastases (BSBM) [4].

Material and Methods

We analyzed patients from a previously described brain metastases database, which is maintained and updated at the first author's institution [5,6]. All patients were newly diagnosed and treated outside of clinical trials (ie, according to routine clinical practice) at two different institutions in Norway (a university hospital and an academic teaching hospital, respectively) and one in Germany (a university hospital) in the time period between January 01, 1983 and October 01, 2011. No active trials were available for patients with brain metastases during this time period. For this retrospective study, all patients with primary tumours eligible for computation of the DS-GPA were selected (n=412). Complete information on all parameters necessary to assign this score was required (eg, biological subtype in cases with breast cancer [basal, luminal A or B, HER2]). Treatment was individualized (eg, WBRT, surgery, SRS and combinations thereof).

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Table 1. Comparison of the prognostic scores evaluated in this study, empty fields indicate that a parameter is not used in the index.

Score	Performance status	Age	Extracranial metastases	Controlled primary	Number of BM	Class I	Class II	Class III	Class IV
BSBM	KPS 80–100: 1 point KPS ≤70: 0 points		no: 1 point yes: 0 points	yes: 1 point no: 0 points		3 points	2 points	1 point	0 points
GPA	KPS 90–100: 1 point KPS 70–80: 0.5 points KPS <70: 0 points	<50: 1 point 50–59: 0.5 points >60: 0 points	none: 1 point present: 0 points		1: 1 point 2–3: 0.5 points >3: 0 points	3.5–4 points	3 points	1.5–2.5 points	0–1 points
DS-GPA GI	KPS 100: 4 points KPS 90: 3 points KPS 80: 2 points KPS 70: 1 point					3.5–4 points	2.5–3 points	1.5–2 points	0–1 points
DS-GPA Breast*	KPS 90–100: 1.5 points KPS 70–80: 1 point KPS 60: 0.5 points	<60: 0.5 points							
DS-GPA Lung	KPS 90–100: 1 point KPS 70–80: 0.5 points	<50: 1 point 50–60: 0.5 points	none: 1 point		1: 1 point 2–3: 0.5 points				
DS-GPA MM and RCC	KPS 90–100: 2 points KPS 70–80: 1 point				1: 2 points 2–3: 1 point				

BM – brain metastases; KPS – Karnofsky performance score' BSBM – basic score for brain metastases; GPA – graded prognostic assessment; DS-GPA – diagnosis-specific GPA; GI – gastrointestinal primary tumours; MM – malignant melanoma; RCC – renal cell carcinoma. * Add 1 point for luminal A primary tumour type, 1.5 points for Her-2, and 2 points for luminal B.

Table 2. Pretreatment characteristics of all 412 patients included in this study.

Parameter	Number	Percent
Primary cancer type		
Breast cancer	37	9
Lung cancer	226	55
Renal cell cancer	40	10
Gastrointestinal cancer	50	12
Malignant melanoma	59	14
Extracranial metastases		
Absent	135	33
Present	277	67
Primary tumour control		
Controlled	245	59
Uncontrolled	167	41
Number of brain metastases		
One	151	37
Two or three	130	32
More than three	131	32
Sex		
Female	153	37
Male	259	63
Time period		
1983–1989	103	25
1990–1999	108	26
2000–2011	201	49
Median Karnofsky performance status	70 (range 30–100)	
Median age, years	60 (range 23–93)	

The study from the United States and Canada also included all different therapeutic approaches and patients who were treated in the time period between 1993 and 2010 [1]. Actuarial survival from first day of treatment was calculated with the Kaplan-Meier method and compared between different groups with the log-rank test. This approach was used to evaluate the prognostic impact of baseline parameters in univariate analyses. For multivariate analysis of survival, Cox regression analysis was used. A p-value ≤ 0.05 was considered statistically significant. The PASW Statistics 18 software package (IBM SPSS Statistics, Somers, NY, USA) was used for the statistical analyses. After determining prognostic factors, established scores (BSBM, GPA, DS-GPA) were computed as previously described [1,2,4]. The performance of these three scores was tested in all 412 patients. Then, DS-GPA was validated for each diagnosis group (ie, patients with breast cancer, malignant melanoma, renal cell carcinoma, gastrointestinal cancers and lung cancers). Thirty-one patients (7.5%) were alive at last follow-up (January 01, 2012), with a median follow-up of 11.5 months (range 3–52). These patients were censored, while length of survival was known in all other patients. The baseline characteristics are shown in Table 2.

Results

Median survival of all 412 patients was 3.6 months. Patients managed with primary surgery or SRS with or without additional WBRT (n=79, 19%) had median survival of 11.0 months as compared to 3.1 months with primary WBRT (n=333, 81%), p=0.0001. In further univariate analyses of baseline parameters, primary tumour type was also associated with survival (breast cancer was most favorable, with median 7.0 months; gastrointestinal tumours were least favorable, with median 3.3 months, p=0.01). Moreover, Karnofsky performance status (KPS), age, number of brain metastases, presence of extracranial metastases and primary tumour control all were significant prognostic factors (p=0.008 or less). KPS, age and number of brain metastases were significant regardless of whether they were analyzed as continuous or categorical variables, stratified as described in the DS-GPA study (ie, KPS <70, 70–80, 90–100; age <50, 50–60, >60 years; number of brain metastases 1, 2–3, >3). In multivariate analysis, KPS, extracranial metastases and primary tumour control were the most important prognostic factors (all p=0.0001), followed by number of brain metastases (p=0.001), age (p=0.08) and primary tumour type (p=0.55). However, regarding the different diagnosis strata, (ie, primary breast cancer, malignant melanoma, renal cell carcinoma, gastrointestinal cancers and lung cancers), important differences in prognostic factors existed. Table 3 shows the multivariate analysis for patients with malignant melanoma. Identical to the previous study [1], only two factors correlated significantly with survival – KPS and number of brain metastases. The results of all other strata differed from those found in the study by Sperduto et al. [1] (Table 4).

All three prognostic scores predicted survival, with highly significant global p-values of 0.0001 (over all strata). The Kaplan-Meier curves are shown in Figures 1–3. However, pairwise rather than global comparison of all prognostic strata revealed different results. Here it was shown that GPA failed to achieve a significant difference between class I and II (ie, patients in the best prognostic groups) p=0.7. In contrast, all p-values for pairwise comparison of the BSBM and DS-GPA classes were statistically significant. Median survival by DS-GPA strata was 2.7, 3.6, 7.0 and 11.3 months in the 4 groups with 0–1, 1.5–2, 2.5–3 and 3.5–4 points, respectively. DS-GPA significantly predicted survival in all diagnosis strata (ie, in patients with primary breast cancer, malignant melanoma, renal cell carcinoma, gastrointestinal cancers and lung cancers) (Kaplan-Meier curves not shown).

Discussion

This multi-institutional study attempted for the first time to confirm the usefulness of DS-GPA in European patients. As in the study from the United States and Canada, patients treated with all different local approaches were included,

Table 3. Prognostic factors in patients with malignant melanoma (multivariate Cox regression analysis). Omnibus tests of model coefficients: –2 log likelihood 322.85, chi-square 18.93, df 4, significance 0.0001.

Variables	B	SE	Wald	df	p-value	Exp(B)
KPS*	–0.70	0.23	8.99	2	0.003	0.49
Age*	0.05	0.18	0.08	2	0.779	1.05
Number of brain metastases*	0.43	0.19	5.25	2	0.022	1.54
Extracranial metastases	0.32	0.46	0.47	1	0.493	1.37

KPS – Karnofsky performance status. * Categorical variables (defined as described by Sperduto et al. [1] and also in the text).

Table 4. Comparison of the statistically significant prognostic factors stratified by primary diagnosis. Primary tumour control was not included in these multivariate analyses.

Primary tumour type	Present study	Sperduto et al. [1]
Lung cancer	KPS, age	KPS, age, number of BM, extracranial metastases
Breast cancer	KPS	KPS, age, histology
Renal cell cancer	Extracranial metastases, number of BM	KPS, number of BM
Gastrointestinal primary	KPS, extracranial metastases, number of BM	KPS
Malignant melanoma	KPS, number of BM	Identical

KPS – Karnofsky performance status; BM – brain metastases.

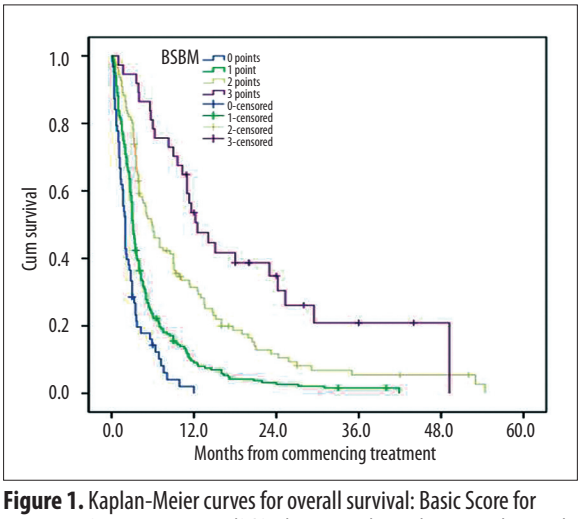

Figure 1. Kaplan-Meier curves for overall survival: Basic Score for Brain Metastases (BSBM) 0 points (n=62), 1 point (n=202), 2 points (n=111) and 3 points (n=37), p=0.0001 (global over all strata), also significant for pairwise comparisons. Assign 1 point each for controlled primary tumour, absence of extracranial metastases and Karnofsky performance status 80-100 to compute this score.

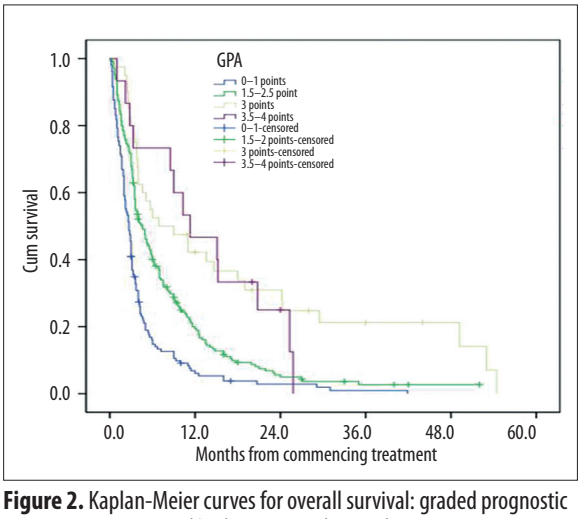

Figure 2. Kaplan-Meier curves for overall survival: graded prognostic assessment (GPA) 0–1 point (n=153), 1.5–2 points (n=204), 2.5–3 points (n=40) and 3.5–4 points (n=15), p=0.0001 (global over all strata), no significant difference between the two groups with best prognosis.

and those managed with best supportive care were excluded [1]. However, primary surgery or SRS were used in only 19% of all European patients. This fact, which very likely reflects differences in baseline characteristics, such as number of lesions and performance status, makes the present patient population more representative of real-world patients with brain metastases. For example, 36% of our patients belonged to the unfavorable group with 0–1 points (16% in the other study), and 7% to the best group with 3.5–4 points (14% in the other study). The vast majority of our patients had symptomatic rather than screening-detected brain metastases. Especially in Norway, screening of asymptomatic patients was uncommon, except for initial staging in those with newly diagnosed lung cancer. Another important difference between the two studies is the number of cases (3,940 *vs.* 412). Both studies share some weaknesses, such as lack of documentation of brain metastases size, blood chemistry anomalies or systemic cancer therapy, which also could influence prognosis [7–9].

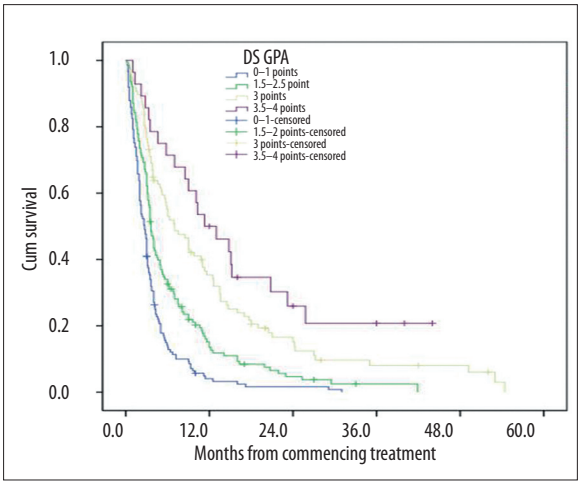

Figure 3. Kaplan-Meier curves for overall survival: diagnosis-specific graded prognostic assessment (DS-GPA) 0–1 point (n=148), 1.5–2 points (n=139), 2.5–3 points (n=97) and 3.5–4 points (n=28), p=0.0001 (global over all strata), also significant for pairwise comparisons.

Our results confirm the validity of the DS-GPA score for each of the primary diagnosis strata and also for all patients combined, notwithstanding differences in multivariate analyses of prognostic factors (Table 4). In our analysis of all 412 patients, the initial GPA score [2] performed less well, while the BSBM score [4] was equivalent to DS-GPA. However, BSBM does not acknowledge the differences in natural history and biology of the different primary cancers. Moreover, it requires assessment of primary tumour control, which is a controversial, albeit statistically significant, prognostic factor. While the importance of uncontrolled large lung cancers, which might cause fatal bleeding, pneumonia and other life-threatening problems, is obvious, that of uncontrolled breast cancers or malignant melanoma is less convincing. It is also difficult to define exactly what degree of response to previous treatment is required in order to fulfil the definition of unequivocal local control. Adoption of the DS-GPA score might be preferable, not only because it circumvents assessment of the primary tumour status.

Median survival of our patients was 3.6 months, which is clearly shorter than that of the patients in the other DS-GPA study (7.2 months) [1]. This finding was true for each of the diagnosis strata (eg, median survival of 7.0 *vs.* 13.8 months) in patients with breast cancer. Survival differences were smaller in patients with unfavorable prognosis, such as those with 0–1 points (median 2.7 *vs.* 3.1 months) as compared to those with favorable prognosis, such as those with 3.5–4 points (median 11.3 *vs.* 16.7 months). A likely explanation is that different management patterns might impact survival predominantly in patients with better prognosis. In other words, patients with good performance status and brain-only disease will only become long-term survivors if death from uncontrolled brain metastases can be prevented. Median survival after WBRT was 3.1 months in our study. Largely comparable figures were reported from the previous study (eg, 2.9 months in patients with gastrointestinal cancers and malignant melanoma or 3.5 months in those with non-small-cell lung cancer treated with WBRT) [1]. The increased use of surgery or SRS in the United States and Canada has probably resulted in improved survival in patients who were eligible for such treatment. This hypothesis is in accordance with evidence from randomized trials of WBRT alone *vs.* WBRT plus additional surgery [10] or SRS [11] and case-control studies [12,13]. Recent guidelines for the management of single brain metastases recommend surgery or SRS for most scenarios, whereas their role is less well defined in patients with more than one brain metastasis [14–17]. Our own data, which are retrospective in nature and therefore subject to potential selection bias, indirectly confirm that aggressive local management should be considered in patients with a limited number of accessible or SRS-eligible brain metastases, provided extracranial disease activity does not limit survival to less than 3–4 months. Another factor that might have influenced the observed difference in median survival between the study from the United States and Canada and our own is inclusion of historical patients who were treated during the 1980s.

Conclusions

It should be noted that the DS-GPA score is not perfect in predicting survival. Even in the two most favorable groups, occasional patients survive for less than 3 months. Moreover, in the unfavorable group, survival beyond 12 months has been recorded as well. In other words, marked heterogeneity in outcomes for patients with brain metastases exists, comparable to the situation in other oncology scenarios [18–20]. The challenge is to assign the right patient to the right treatment, with clear objectives set up-front, such as palliation of symptoms in the terminal phase of disease or effective local control in cases with a single lesion. The DS-GPA score might improve shared decision making. The RTOG has also adopted this score as a stratification parameter in ongoing clinical trials [1].

Conflict of interest statement

None declared. No other acknowledgements.

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