



Validation and comparison of Breast Graded Prognostic Assessment scores in patients with breast cancer and brain metastases

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Abstract

Purpose Brain metastases (BM) occur in 15–35% of patients with metastatic breast cancer, conferring poor prognosis and impairing quality of life. Clinical scores have been developed to classify patients according to their prognosis. We aimed to check the utility of the Breast Graded Prognostic Assessment (B-GPA) and its modified version (mB-GPA) and compare them in routine clinical practice.

Methods This is an ambispective study including all patients with breast cancer BM treated in a single cancer comprehensive center. We analyzed the overall survival (OS) from BM diagnosis until death. The Kaplan–Meier method and Cox proportional hazard regression model were used in the analyses. ROC curves were performed to compare both scores.

Results We included 169 patients; median age was 50 years. HER2-positive and triple negative patients were 33.7% and 20.7%, respectively. At the last follow-up, 90% of the patients had died. Median OS was 12 months (95% confidence interval 8.0–16.0 months). OS was worse in patients with > 3 BM and in patients with triple negative subtype.

Conclusions In our series, we confirm that B-GPA and mB-GPA scores correlated with prognosis. ROC curves showed that B-GPA and mB-GPA have similar prognostic capabilities, slightly in favor of mB-GPA.

Keywords Breast cancer · Brain metastases · Prognosis · Breast Graded Prognosis Assessment · Survival outcomes

Introduction

Brain metastases (BM) are associated with functional deterioration and poor prognosis. Reports on the natural history of the disease found a median overall survival (OS) of 1 month if no treatment was given [1]. Before the

development of targeted drugs and despite whole-brain radiotherapy (WBRT), median OS in the last century was less than 6 months [2]. However, BM in patients with breast cancer (BC) encompasses a wide range of prognostic groups of patients, all of whom require different approaches. Indeed, prognosis in some patients is fatal, while others might achieve more than 3 years of survival [3–6]. Among patients with advanced BC, up to 50% of those with HER2-positive disease and approximately 30–50% of patients with triple negative disease (TNBC) will develop BM. In contrast, about 10–15% of patients with hormone receptor (HR)-positive tumors will develop BM during the course of their disease [7, 8]. Median OS is about 24, 10 and 7 months for HER2⁺, HR⁺ and TNBC patients, respectively [6, 9].

The development of anti-HER2 drugs has substantially improved the survival outcomes of HER2-positive BC patients [10–12]. However, the penetration of some of these drugs across the blood–brain barrier is assumed to be limited, so many of these patients end up developing BM. Moreover, more accurate treatment strategies have emerged in recent years [13, 14]. This phenomenon, together with

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improved diagnostic imaging techniques, has led to the detection of an increase in BM incidence in all subtypes [15], prompting current efforts focusing on BM control.

Efforts must be made to improve survival while avoiding toxicities in patients with limited life expectancy. The addition of whole-brain radiation delays progression, but at the same time that improves overall survival, it also impairs cognitive function and, therefore, quality of life [16]. Because of this, in patients with a limited number of lesions, in a location amenable to brain surgery or stereotactic radiosurgery (SRS), those strategies are the preferred treatment options, since they minimize brain toxicity [17–21].

Several prognostic factors have been described in patients with BC and BM. The most important factors are performance status, tumor subtype, age and comorbidities. Other prognostic factors include the presence of active extracranial disease and, more recently, the number of BM [4, 22–25]. Prognostic predictor tools that include some of the clinical and histological factors described above have been developed to tailor treatment according to prognosis and efficacy of these treatments [25, 26]. The Breast Graded Prognostic Assessment (B-GPA) is a well-known score for assessing the prognosis of patients with BC and BM. The B-GPA proved to be more accurate than the traditional recursive partitioning analysis (RPA) score [27]. The B-GPA was later adapted by the same group to include other prognostic factors such as BC subtype, Karnofsky Performance Scale (KPS), and age at diagnosis of BM [4, 23, 25]. Despite its good correlation with survival, the B-GPA does not consider the number of BM. This issue is important as it determines suitability for local treatments such as SRS or surgery. In 2015, Subbiah et al. proposed a modified B-GPA score (mB-GPA) which includes the number of BM, proving the value of the new score in predicting the survival of these patients [5].

Some authors have attempted to validate these scores in different populations, but more evidence is needed to confirm their utility, and to determine which is the best score in this setting [3–5, 23–26, 28, 29]. The primary aim of our study was to validate the B-GPA and mB-GPA in routine clinical practice in a consecutive series of BC patients with BM treated at a single Spanish comprehensive cancer center. The secondary aim was to compare both scores to determine which is best for making clinical decisions.

Materials and methods

Study design and patients

This is an ambispective study of patients with BC and BM treated in a single comprehensive cancer center in Spain between January 2003 and April 2019. Inclusion criteria were: histologically proven invasive BC, age > 18 years at the time of BC diagnosis, BM confirmed by brain magnetic resonance imaging (MRI) or cerebral computed tomography scan. Patients with leptomeningeal disease were excluded unless they had concomitant BM. All subjects included prospectively gave their informed consent for inclusion in the study. The Ethics Committee also allowed the analysis of deceased patients. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of University Hospital of Bellvitge (PR189/20). Clinical data were collected retrospectively until 2014, and prospectively from 2014 to 2019.

Clinical and pathological data were collected for each patient, including patient demographics, KPS, number of BM, symptoms related to BM, BC subtype, histological grade, local and systemic treatments administered and response to each one. Estrogen receptor (ER), progesterone receptor (PR) and HER2 expression were determined by immunohistochemistry (IHC). Positivity for HR was defined as any receptor IHC spotting in at least 1% of tumor cells. HER2 status was defined as positive if IHC score 3+ or 2+ and amplification by fluorescent in situ hybridization (FISH). According to IHC and FISH, patients were classified into three subtypes: TN (HR⁻/HER2⁻), luminal-like (HR⁺/HER2⁻) and HER2⁺ (HR⁺ or ⁻/HER2⁺).

Statistical analysis

B-GPA and mB-GPA scores [4, 5] were calculated for each patient (Table 1), classifying them into four groups. A higher score represents a better prognosis from 0 to 4 points.

Descriptive statistics were performed for demographic and clinical characteristics of the patients including sex, age and performance status at BM diagnoses, tumor subtype, stage at diagnosis, number of BM and BM treatment.

OS was defined as the time from BM diagnoses to death due to any cause. The Kaplan–Meier method was used to calculate OS and univariate analyses were conducted using the Cox proportional hazard regression model to calculate hazard ratios and 95% confidence intervals (CI).

Table 1 B-GPA and mB-GPA scores

B-GPA score					
Factor	0	0.5	1.0	1.5	2.0
KPS	≤ 50	60	70–80	90–100	
BC subtype	TN	–	HR ⁺ /HER2 ⁻	HR ⁻ /HER2 ⁺	HR ⁺ /HER2 ⁺
Age (years)	≥ 60	< 60			
mB-GPA score					
Factor	0	0.5	1.0	1.5	2.0
KPS	≤ 50	60	70–80	90–100	
BC subtype	TN	HR ⁺ /HER2 ⁻	HR ⁻ /HER2 ⁺	HR ⁺ /HER2 ⁺	
Age (years)	> 50	≤ 50			
Number of BM	> 3	1–3			

B-GPA Breast Graded Prognostic Assessment, *mB-GPA* modified Breast Graded Prognostic Assessment, *KPS* Karnofsky performance status scale, *BC* breast cancer, *TN* triple negative, *HR* hormone receptor, *BM* brain metastases

Survival ROC curves were constructed to compare both scores to determine which correlated better with OS. Data analysis was performed using IBM SPSS version 18 and R software version 3.3.3.

Results

Patient characteristics

A total of 169 patients seen between January 2014 and April 2019 were included, all of whom were women. The median KPS was 80% [interquartile range (IQR) 70–90%]. Patient characteristics are listed in Table 2.

Most patients (54%) received multimodal treatment with surgery, SRS and/or WBRT. Patients who received multimodal treatment had a median KPS of 90% (IQR 90–100%), while patients who received only WBRT had a median KPS of 80% (IQR 70–90%). At a median follow-up of 12 months (0–162 months), 90% of the patients had died. Median OS was 12 months (95% CI 8.0–16.0). Median OS accordingly to tumor subtype was 26 months, 11 months and 8 months in HER2-positive, luminal and TNBC patients, respectively ($p=0.01$ in the univariate analysis). OS was 22 months in patients with one BM, 11 months in those with 2–3 BM, and 8 months in patients with > 3 BM ($p=0.046$). No other clinical and biological factors analyzed correlated with OS. There were no significant differences in patients diagnosed before 2010 or later.

B-GPA and mB-GPA score validation and comparison

Both B-GPA and mB-GPA scores were significant predictors of OS with a p value < 0.005 (Fig. 1). Table 3 shows median OS with confidence intervals for each group for both scores. Median OS was 6, 6, 17 and 24 months in patients with B-GPA scores ranging from 0–1.0, 1.5–2.0, 2.5–3.0 and 3.5–4.0, respectively, while median OS was 4, 7, 26 and 30 months in patients with mB-GPA ranging from 0–1.0, 1.5–2.0, 2.5–3.0 and 3.5–4.0 respectively.

The survival ROC curves for B-GPA and mB-GPA were very similar, showing a slightly higher AUC for the mB-GPA curve (B-GPA AUC: 0.269 vs. mB-GPA AUC: 0.286).

Discussion

Our study showed that both B-GPA and mB-GPA scores are useful tools for predicting OS in BC patients with BM, identifying a subgroup of patients with better survival outcomes. However, mB-GPA seemed to be a better prognostic tool, since it showed a slightly higher AUC and it seemed to better discriminate than B-GPA among patients with worse prognoses (OS of 4 vs. 7 months using mB-GPA and 6 vs. 6 months using B-GPA for patients with 0–1 vs. 1.5–2 points, respectively). Likewise, mB-GPA discriminates better the two top prognosis groups classified showing better survival and higher differences than B-GPA when giving the same punctuation (OS of 26 using mB-GPA and 17 months using B-GPA for patients with 2.5–3 points). The addition of the number of BM can help us to decision-making.

Table 2 Patient and tumor characteristics ($N=169$)

Characteristic	Median	Range	
Age at BM diagnosis (years)	50	29–81	
Characteristic	Groups	<i>n</i>	%
KPS	< 70	21	12.4
	70–80	77	45.6
	90–100	69	40.8
	Unknown	2	1.2
Tumor type	HER2-positive	57	33.7
	Luminal-like HER2-negative	66	39.1
	Triple negative	35	20.7
	Unknown	11	6.5
Stage IV at diagnoses	Yes	37	21.9
	No	109	64.5
	Unknown	23	13.6
Number of BM	1 lesion	53	31.4
	2–3 lesions	57	33.7
	> 3 lesions	53	31.4
	Unknown	6	3.6
BM treatment	Surgery alone	5	3.0
	SRS alone	12	7.1
	WBRT alone	77	45.6
	Surgery + SRS	3	1.8
	SRS + WBRT	16	9.5
	Surgery + WBRT	23	13.6
	Only systemic treatment	10	5.9
	No treatment	12	7.1
	Unknown	11	6.5
Progression after BM treatment	Only systemic	94	55.6
	Only brain	32	18.9
	Both brain and systemic	33	19.5
	Unknown	10	5.9
Leptomeningeal metastases	Yes	37	21.8
	No	128	75.3
	Unknown	5	2.9

KPS Karnofsky performance status scale, BM brain metastases, WBRT whole brain radiotherapy, SRS stereotactic radiosurgery

Our series has similar characteristics to those described in the literature for BC patients with BM [3–5, 29]. All patients were women with a median age of 50 years, mostly HER2⁺ and HR⁺, with a KPS greater than 70%. In the univariate analysis, our study confirms the predictive value of both the BC subtype and the number of BM, as shown in many other studies [3, 5, 29].

Regarding systemic treatment, advances in effective new targeted therapies in HER2⁺ and HR⁺ patients are leading to improvements in both PFS and OS [30–36], but they do not seem effective in preventing BM [37]. Knowledge is rapidly expanding, and novel and promising anti-HER2 targeted drugs, such as tucatinib and neratinib, have emerged to treat BM in HER2⁺ BC [13, 38–40].

Table 3 Overall survival by B-GPA and mB-GPA

B-GPA	<i>n</i>	OS (months)	95% CI (months)	
0–1	18	6	0.4–11.6	<i>p</i> < 0.001
1.5–2	37	6	4.3–7.7	
2.5–3	61	17	10.5–23.5	
3.5–4	47	24	16.6–31.4	
Missing	6			
mB-GPA	<i>N</i>	OS (months)	95% CI (months)	
0–1	18	4	0.2–7.8	<i>p</i> < 0.001
1.5–2	60	7	5.1–8.9	
2.5–3	68	26	20.1–31.8	
3.5–4	17	30	19.2–40.8	
Missing	6			

B-GPA Breast Graded Prognostic Assessment, *mB-GPA* modified Breast Graded Prognostic Assessment, *SBM* survival after brain metastases, *CI* confidence interval

An established prognostic index can assist in selecting the best approach for each patient, taking into account all of these characteristics and expected survival after BM diagnosis. We compared B-GPA with mB-GPA using survival ROC curves, and found that the mB-GPA index was slightly superior in predicting SBM. This result, in line with the results of the previous studies and validation cohorts [3–5, 29], supports the use of mB-GPA in routine clinical practice for the appropriate stratification of patients and therapeutic decision-making.

Extracranial disease status has been proposed as a prognostic factor which could help determine the most suitable treatment [29]. Nevertheless, clinical guidelines recommend beginning by treating the affected areas that involve a risk to life [41]. That means extracranial involvement determines the timing more than the kind of treatments, so it was not taken into account in most of the studies [4, 23, 26].

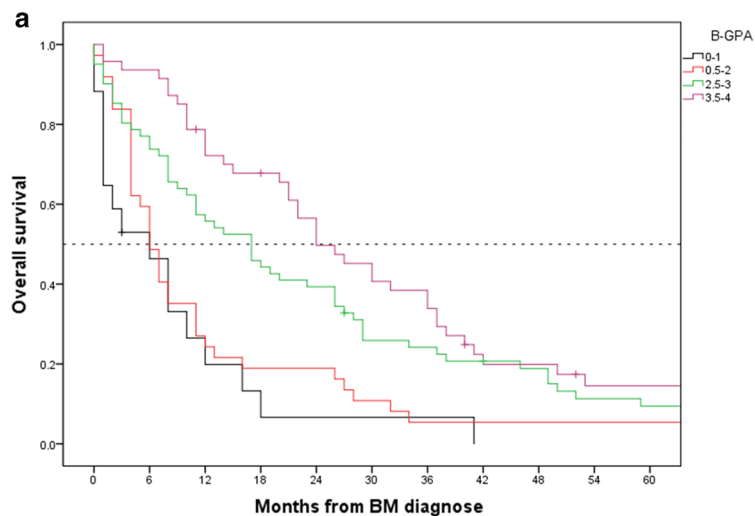
This study has several strengths and limitations. It has a large sample size and long-term follow-up among breast cancer patients treated in a single Spanish comprehensive cancer center. We are aware, however, that almost 50% of the patients were included retrospectively, so not all the information regarding those patients was available and we

could have been missing. We decided to include all patients to minimize the selection bias. Moreover, all patients were treated at the same institution, in the multidisciplinary Neuro-Oncology Unit (NOU), where patients are evaluated by different specialists involved in the management of patients with primary and secondary brain tumors. The use of these prognostic indexes, in combination with the decisions of the NOU committee, is helping us to determine the best therapeutic strategies for our BC patients with BM.

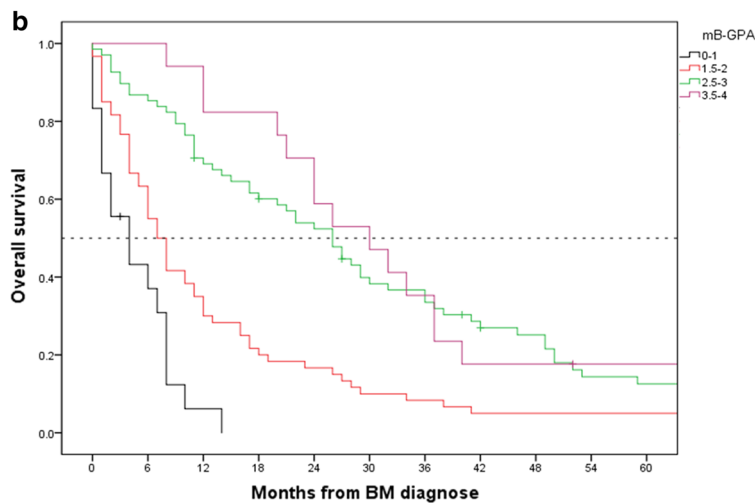
Conclusions

Our study validates previous results regarding the GPA scores for discriminating risk groups with significant different survival outcomes in patients with breast cancer and brain metastases. In the univariate analysis, B-GPA and mB-GPA, number of lesions, and tumor subtype were the most important prognostic factors mB-GPA, in conjunction with evaluation by a multidisciplinary team, can help select the best approach and adjust the therapeutic effort in each patient.

Fig. 1 The Kaplan–Meier curves show that the OS can be ranked using either B-GPA (a) and mB-GPA (b). The *p* value was <0.005 for both scores. Patients with higher punctuation had longer survival in the two models. A higher punctuation than two is correlated with more than 1 year and a half of median overall survival in B-GPA score and more than 2 years in mB-GPA score



B-GPA	No. of patients at risk										
	0	6	12	18	24	30	36	42	48	54	60
0-1	17	8	4	2	1	1	1	0	0	0	0
1.5-2	37	22	10	7	7	4	2	2	2	2	2
2.5-3	61	47	35	28	24	15	14	12	10	6	5
3.5-4	47	44	36	31	25	20	17	9	8	5	5



mB-GPA	No. of patients at risk										
	0	6	12	18	24	30	36	42	48	54	60
0-1	18	7	1	0	0	0	0	0	0	0	0
1.5-2	60	38	21	13	10	6	5	3	3	3	3
2.5-3	68	59	47	41	35	25	23	17	14	8	7
3.5-4	17	17	16	14	12	9	6	3	3	2	2

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12094-021-02577-x>.

Author contributions AS, JL, MG, SR, MB and CF conceived and planned the hypothesis. MG, MS, RV and SP improved the overview of the study. AS, JL, SR, MB and CF planned the study protocol and collected the data. VN, AS and CF analyzed the data and presented the results. CF took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and writing of the manuscript.

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Data availability Database encompassing all patient data is saved in the Hospital's hardware.

Code availability IBM SPSS version 18 and R software version 3.3.3.

Declarations

Conflict of interest MG declares consulting/advisory fees from Pfizer, Eisai, Genomic-Health, Agendia, Daiichi-Sankyo, Novartis, Roche Pharma and Kern and travel/accommodation grants from Daiichi-Sankyo, Kern, Novartis and Pfizer. SP declares consulting/advisory fees from Astra-Zeneca, Daiichi-Sankyo, Novartis, Polyphor and Roche and travel/accommodation grants from Novartis. CFZ declares facilities to congress attendance from Pfizer. RVV declares professional fees from Novartis, Pfizer and Roche. RVF declares professional fees from Novartis, Gilead, Eisai, Esteve and Takeda. The rest of the authors have no conflicts of interest to declare.

Ethical approval The protocol and the informed consent were approved by the Ethics Committee of University Hospital of Bellvitge (PR189/20). (Appendix 1 in ESM).

Consent to participate Patients included prospectively signed the informed consent approved by ethics committee (Appendix 2 in ESM).

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