Original Article

Validation of Modified Breast Graded Prognostic Assessment for breast cancer patients with brain metastases: extra-cranial disease progression is an independent risk factor

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Background: Breast cancer (BC) patients with brain metastases (BM) are heterogeneous with markedly variable survival. The Breast Graded Prognostic Assessment (B-GPA) and Modified B-GPA (mB-GPA) have been proposed as useful tools for stratifying survival in this population. However, extra-cranial disease progression, a clinically important variable, is not incorporated into the final model. We undertook the validation of B-GPA and mB-GPA in an Asian cohort and further explore extra-cranial disease progression as a prognostic factor.

Methods: Data of BC patients with newly diagnosed BM between 2006 and 2017 was extracted retrospectively from a prospectively maintained institutional database. Patients were classified based on their B-GPA and mB-GPA scores. Univariate (UVA) and multivariate analysis (MVA) using the Cox proportional hazard model were performed to investigate the factors prognostic of overall survival (OS). The Kaplan-Meier method was used to estimate OS and log-rank test to compare survival between scores. The performances of B-GPA and mB-GPA were compared using Harrell's concordance index (C-index) and Akaike information criterion (AIC).

Results: In our cohort of 282 patients, the B-GPA and mB-GPA were validated as prognostic tools for OS, demonstrating excellent separation between survival curves (P<0.001). In MVA, we found all components of mB-GPA (age, performance status, number of BM, tumour subtype) to be independent predictors of survival. C-index was 0.64 and AIC was 2,483.39 for B-GPA. mB-GPA demonstrated marginally better discrimination with a C-index of 0.65 and AIC of 2,445.78. Extra-cranial progression was an independent predictor for survival in our population (P<0.001).

Conclusions: The mB-GPA incorporates four simple clinical variables each of independent prognostic significance. Both B-GPA and mB-GPA demonstrate moderate discriminative capabilities for OS with mB-GPA performing marginally better. Inclusion of extra-cranial disease progression as a factor in future model development may further improve its prognostic value.

Keywords: Breast cancer (BC); brain metastases (BM); prognostication; extra-cranial progression; radiotherapy

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Introduction

Central nervous system (CNS) metastases are a serious complication of solid organ tumours, resulting in significant morbidity and mortality (1). Breast cancer (BC) is the second most common cause of brain metastases (BM) (2). Previously regarded as having a uniformly dismal prognosis, advances in treatment have resulted in the recognition that BC patients with BM are heterogeneous with widely differing survival (3-5). Factors found to prognosticate survival in these patients include performance status, age, number of BM, tumour histology, receipt of local or systemic therapy and extra-cranial disease status (6-10). Various prognostic instruments incorporating these factors have been developed (11-14).

The Graded Prognostic Assessment (GPA) is one of the better-known prognostic instruments (15).

Originally developed from a database of 1,960 patients with BM accrued from five Radiation Therapy Oncology Group (RTOG) trials, this instrument was notable for its exclusion of systemic disease control as a variable as the authors viewed the lack of precision in determining "disease control" a limitation (16-19). The GPA was further refined in subsequent years. Starting with the development of disease-specific GPA (DS-GPA) for specific cancer subtypes using a multi-institutional analysis of 4,259 patients with BM, the authors went on to refine the Breast Cancer Specific GPA (B-GPA) by analysing a sample of 400 patients with BC and BM (20-22). Further modification to produce the Modified Breast-GPA (mB-GPA) has recently been proposed by integrating the number of BM as an additional variable (23).

The primary aim of our study is to validate the B-GPA and mB-GPA in Asian BC patients treated at a single tertiary institute.

The secondary aim is to explore extra-cranial disease progression as a prognostic factor in our population as patients with BM often have co-existing extracranial disease that can have major impact on survival, regardless of intracranial disease control (24).

Methods

Female patients 18 years or older with histologically proven BC and newly diagnosed intra-parenchyma referred for radiotherapy between 1st January 2006 and 31st October 2017 were retrospectively identified from an institutional database. Patients diagnosed before 2006 were excluded as HER-2 status was not routinely tested for and Trastuzumab was not widely available. Patients with incomplete information or recurrent BM were excluded.

Clinical and biological information including patient demographics, Karnofsky Performance Score (KPS), treatment received, extra-cranial disease progression and other tumour characteristics were extracted from patient's medical records.

Patients were classified into four BC subtypes: "Basal" (ER–/PR–/HER2–), "Luminal A" (ER and/or PR+, HER2–), "Luminal B" (ER and/or PR+, HER2+) and "HER2 Enriched" (ER/PR–, HER2+). Overall survival (OS) was measured from date of radiotherapy completion to the date of death. If no treatment was given, OS was measured from date of BM diagnosis to the date of death. Patients without events were censored at the date of their last follow-up.

We counted the number of BM based on best available brain imaging or radiological reports. Fine-cut MRIs were preferred over CT-scans. We further classified patients based on their extra-cranial disease status. We determined extra-cranial disease status from radiology reports and/or physician assessment documented in clinical notes. Three categories are recognised. Patients with progressive systemic disease seen on concurrent staging scans whilst on systemic therapy were termed "extra-cranial disease progression". Patients with systemic disease status of complete response, partial response or stable disease whilst on systemic therapy were labelled "extra-cranial disease control". Patients who were treatment naive or who had just started treatment without subsequent follow-up scans were termed "newly diagnosed metastatic disease" (25).

Ethics

This study was approved by Singhealth Central Institutional Review Board (CIRB Ref No. 2013/1037/B). Waiver of consent was granted considering the retrospective, non-interventional nature of study.

Statistical analysis

We calculated the B-GPA and mB-GPA scores for each patient and divided the patients into four bands (0.0–1.0, 1.5–2.0, 2.5–3.0 and 3.5–4.0), similar to prior work by the original GPA developers (20,23).

Univariate (UVA) and multivariate analysis (MVA) using the Cox proportional hazard model were performed to

investigate the factors prognostic of OS. The Kaplan-Meier method was used to estimate OS. Analysis was stratified for patients by GPA score bands and log-rank test was used to compare survival between bands. Harrell's concordance index (C-index) was used to assess the discriminating ability of the B-GPA and mB-GPA within our population and Akaike information criterion (AIC) used to compare between models.

Statistical analyses were carried out using IBM SPSS Statistics (version 25. IBM Corp., Armonk, NY, USA) and R software (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria) (26). The survival and survminer packages were utilized to generate the C-index and survival plots respectively. All reported P values were two-sided with significance level set at 5% (P<0.05).

Results

We identified 360 BC patients with BM from January 2006 to October 2017, of which 282 patients satisfied our inclusion criteria. Fifty patients were excluded as they had recurrent BM and 28 were excluded due to incomplete data. Patient and tumour characteristics are summarised in *Table 1*.

The median age at BM diagnosis was 54.5 (IQR, 48.0 to 61.0) years, with 199 patients (70.6%) older than 50 years old. Our population was predominantly Chinese (75.5%). Overall, 110 patients (39.0%) had a KPS of ≤50 and only 14 patients (5.0%) with a KPS of 90–100. We found no significant difference in KPS distribution based on tumour subtype (P=0.88). Patients with extra-cranial disease progression had significantly lower KPS compared to those without extra-cranial disease progression (P<0.05). A large proportion of our population had received prior treatment: 68.4% had chemotherapy, 81.1% of hormone-receptor positive patients had hormonal therapy and 68.3% of HER2 positive patients had targeted therapy. In our cohort, 130 (46.1%) had extra-cranial progression despite receiving standard systemic treatment.

Median follow-up was 4.93 months (IQR, 1.74 to 13.01 months). At the time of analysis, 266 (94.3%) patients had died of which 47 (16.7%) died within 1 month of radiotherapy. Out of the 47 patients, 35 (74.5%) had KPS <50, 35 (74.5%) were >50 years of age, 30 (63.8%) had more than 3 brain metastases and 32 (68.1%) had extra-cranial disease progression. Patients who died within 1 month had significantly lower KPS and a higher proportion had extracranial disease progression in comparison to the rest of the cohort (P<0.05).

All components of the mB-GPA (KPS, age, number of BM and tumour subtype) were significantly associated with survival in multivariate analysis (MVA) (*Table 2*). Additionally, we found extra-cranial progression to be significantly associated with survival in MVA (P<0.001).

Patients were grouped based on their B-GPA and mB-

Table 1 Patient and tumour characteristics

Variable	Category	Frequency (N=282)	Percent (%)
Age at diagnosis, years	≤50	83	29.4
	>50	199	70.6
Karnofsky Performance Score	≤50	110	39.0
	60	93	33.0
	70–80	65	23.0
	90–100	14	5.0
Ethnicity	Chinese	213	75.5
	Malay	49	17.4
	Indian	17	6.0
	Others	3	1.1
Histology	IDC	255	90.4
	Others	27	9.6

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Category	Frequency (N=282)	Percent (%)
Grade	Grade 1	13	4.6
	Grade 2	58	20.6
	Grade 3	154	54.6
	Unknown	57	20.2
Subtype	Basal	59	20.9
	HER2+ve	59	20.9
	Luminal A	100	35.5
	Luminal B	64	22.7
Number of brain metastases	1–3	104	36.9
	>3	178	63.1
Disease status	Extra-cranial disease progression	130	46.1
	Extra-cranial disease control	62	22.0
	Newly diagnosed metastatic disease	90	32.0
Treatment received	No RT	4	1.4
	WBRT only	229	81.2
	SRS +/– WBRT	49	17.4
Chemotherapy received	Yes	193	68.4
	No	72	25.5
	Unknown	17	6.0
Hormone treatment received in ER/PR+ patients (N=164)	Yes	133	81.1
	No	13	7.9
	Unknown	18	11.0
Targeted agents received in HER2+ patients (N=123)	Yes	84	68.3
	No	39	31.7
Original Breast-GPA score	0.0 to 1.0	59	20.9
	1.5 to 2.0	118	41.8
	2.5 to 3.0	92	32.6
	3.5 to 4.0	13	4.6
Modified Breast-GPA score	0.0 to 1.0	102	36.2
	1.5 to 2.0	130	46.1
	2.5 to 3.0	44	15.6
	3.5 to 4.0	6	2.1

SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; IDC, invasive ductal carcinoma; ER, estrogen receptor; PR, progesterone receptor; GPA, Graded Prognostic Assessment.

Table 2 Univariate and multivariate Cox proportional hazards model for overall survival

Variable	Category	Univariate			Multivariable	
		Median OS (95% CI)	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Subtype	Luminal B	6.83 (3.97, 9.69)	Ref	0.29	Ref	0.032
	Luminal A	5.22 (4.29, 6.15)	1.17 (0.84, 1.63)		1.15 (0.83, 1.61)	
	HER2+ve	4.93 (2.88, 6.98)	1.15 (0.79, 1.66)		1.28 (0.87, 1.89)	
	Basal	3.71 (2.20, 5.22)	1.44 (0.99, 2.07)		1.72 (1.18, 2.51)	
Age	≤50	5.32 (2.94, 7.70)	Ref	0.08	Ref	0.002
	>50	4.80 (3.71, 5.89)	1.27 (0.97, 1.65)		1.55 (1.18, 2.05)	
Karnofsky Performance Score	90 to 100	20.24 (0, 57.44)	Ref	<0.001	Ref	<0.001
	70 to 80	15.38 (11.35, 19.41)	1.57 (0.80, 3.08)		1.46 (0.74, 2.90)	
	60	6.08 (4.97, 7.19)	3.08 (1.58, 6.00)		2.85 (1.43, 5.65)	
	≤50	1.87 (1.42, 2.33)	8.38 (4.30, 16.34)		7.30 (3.65, 14.58)	
Number of brain metastases	1 to 3	8.02 (2.99, 13.04)	Ref	<0.001	Ref	0.002
	>3	4.17 (3.33, 5.01)	1.68 (1.30, 2.18)		1.54 (1.16, 2.03)	
Presence of extra-cranial disease Progression	No	8.90 (4.96, 12.84)	Ref	<0.001	Ref	<0.001
	Yes	2.92 (2.07, 3.77)	2.75 (2.12, 3.56)		2.16 (1.65, 2.83)	

Table 3 Breast Graded Prognostic Assessment (B-GPA) and Modified Breast Graded Prognostic Assessment (mB-GPA)

Prognostic factor	Scoring criteria				
	0	0.5	1.0	1.5	2.0
B-GPA					
KPS	≤50	60	70–80	90–100	–
Subtype	Basal	–	Luminal A	HER2	Luminal B
Age, years	≥60	<60	–	–	–
mB-GPA					
KPS	≤50	60	70–80	90–100	–
Subtype	Basal	Luminal A	HER2	Luminal B	–
Age, years	>50	≤50	–	–	–
No. of brain metastases	>3	1 to 3	–	–	–

KPS, Karnofsky Performance Score.

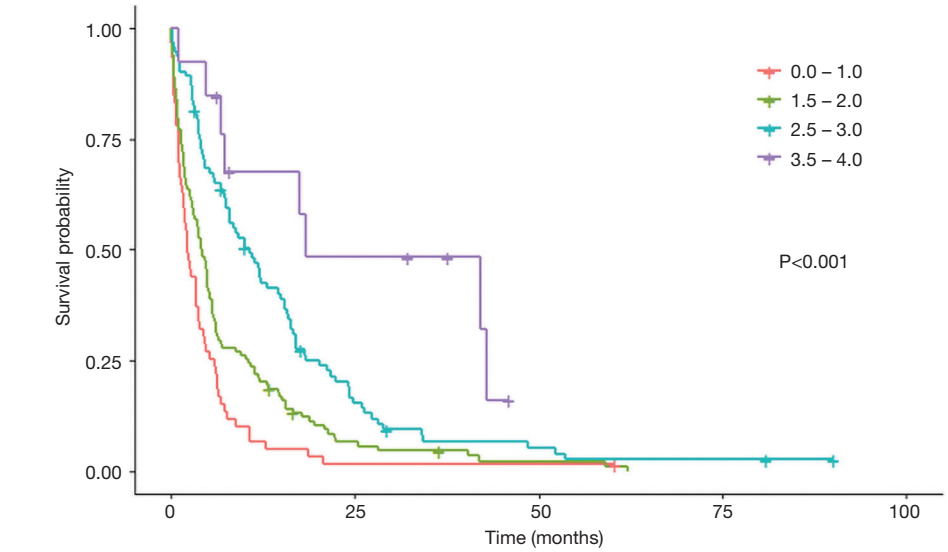
GPA scores (*Tables 1* and *3*). The Kaplan-Meier curve for survival using either scoring systems demonstrated excellent separation between GPA bands (P<0.001) (*Figures 1* and *2*).

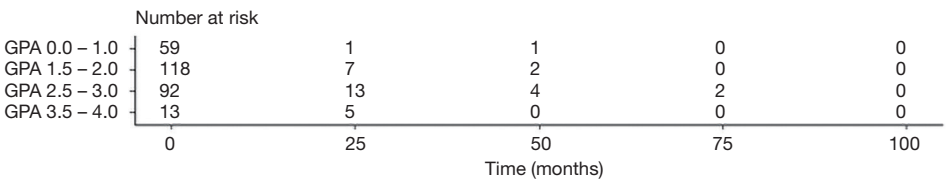
B-GPA

Median OS for patients with B-GPA band 0.0–1.0 was 2.27 months, compared to 4.04, 10.74 and 18.27 months for B-GPA band 1.5–2.0, 2.5–3.0 and 3.5–4.0 respectively (*Figure 1*). C-index was 0.64 and AIC was 2,483.39 for B-GPA.

mB-GPA

Median OS for patients with mB-GPA band of 0.0–1.0





Original Breast GPA Band	Median OS (months) (95% CI)
0.0 – 1.0	2.27 (1.39 to 3.15)
1.5 – 2.0	4.04 (2.93 to 5.15)
2.5 – 3.0	10.74 (7.06 to 14.42)
3.5 – 4.0	18.27 (NA to 46.41)

Figure 1 Kaplan-Meier curve stratified by Original Breast-GPA band. Original Breast-GPA, Original Breast Graded Prognostic Assessment; OS, overall survival; CI, confidence interval; NA, not applicable.

was 2.53 months, compared to 5.75 and 16.89 months for mB-GPA band of 1.5–2.0 and 2.5–3.0 respectively. Estimates of OS for patients with mB-GPA band of 3.5–4.0 was imprecise as there were only 6 patients with 2 events (*Figure 2*). The mB-GPA demonstrated marginally better discrimination than the B-GPA with a higher C-index of 0.65 and lower AIC of 2,445.78.

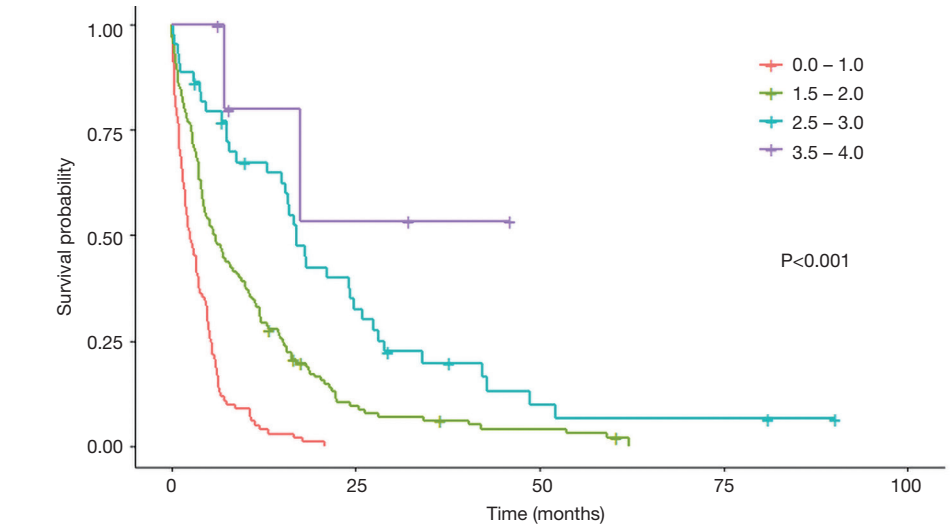
Extra-cranial disease progression

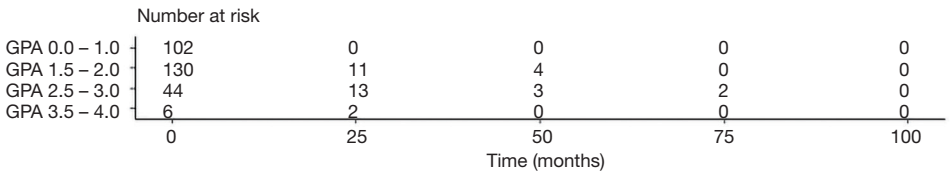
Extra-cranial progression was shown to be a significant predictor of survival on univariate and MVA (multivariate HR 2.16, 95% CI, 1.65–2.83). Patients with extra-cranial progression had a significantly lower median OS of 2.92 months (95% CI, 2.07–3.77) while those with controlled extra-cranial disease or newly diagnosed metastatic disease had a median OS of 8.90 months (95% CI, 4.96–12.84) (*Figure 3*). Including extra-cranial progression as a factor within the mB-GPA model improved its C-index and AIC to 0.69 and 2,419.58 respectively.

Discussion

BC patients with BM are heterogeneous with markedly different survival (3,4,24). Many treatment modalities are available in the care of these patients. The appropriate choice is guided to a significant extent by prognostication.

For patients with favourable prognosis, treatment may include surgery with or without adjuvant radiation, stereotactic radiosurgery (SRS) with or without whole brain radiotherapy (WBRT) or WBRT alone. Patients with poor prognosis may be appropriate for only a short course of WBRT or just supportive care alone as WBRT is not without toxicities and the extent of its clinical benefit





Modified Breast GPA Band	Median OS (months) (95% CI)
0.0 – 1.0	2.53 (1.46 to 3.59)
1.5 – 2.0	5.75 (3.76 to 7.76)
2.5 – 3.0	16.89 (13.92 to 19.86)
3.5 – 4.0	NA

Figure 2 Kaplan-Meier curve stratified by Modified Breast-GPA band. Modified Breast-GPA, Modified Breast Graded Prognostic Assessment; OS, overall survival; CI, confidence interval; NA, not applicable.

remains poorly defined in patients with short survival (27,28). WBRT is known to cause acute toxicities which resolve only gradually with time and tumour shrinkage resulting in clinical improvement that is not immediate. Hence, only patients who can outlive the time required for toxicities to resolve and for clinical improvement to manifest can benefit from WBRT.

For patients who are not expected to live long yet have symptomatic BM requiring WBRT, a shorter course of 12 Gy in 2 daily fractions may be more appropriate and was proven in a British trial not to be inferior to a longer regimen (29). A prospective trial on patients with non-small cell lung cancer with BM who were unsuitable for resection or radiosurgery also showed little overall additional benefit of WBRT over best supportive care. However, improved survival for WBRT was shown for patients younger than 60 years and there was a trend for better outcome in patients with better performance status (30). A similar trial for BC is as yet unavailable.

In our cohort, 47 (16.7%) of our patients had a median survival of less than 1 month after radiotherapy. These patients tended to have poorer function and extra-cranial disease progression. A survival of less than 1 month after cancer treatment is an indicator of poor quality of life (27). Clinicians need to be able to determine a subpopulation of patients whose prognosis remains so guarded that best supportive care is more appropriate.

The original B-GPA model consisted of three factors: KPS, age and tumour subtype (20). It was externally validated in a large cohort of 1,552 BC patients with newly diagnosed BM from 1996 to 2013. Within this validation study, Subbiah *et al.* proposed a modified model by integrating number of BM as a variable. Developed using multivariable Cox regression and recursive partitioning analysis as per prior GPA models, the C-index for the original B-GPA was 0.78 (95% CI, 0.77–0.80) while the C-index for the proposed mB-GPA was 0.84 (95% CI, 0.83–0.85) (23). It has since received two independent

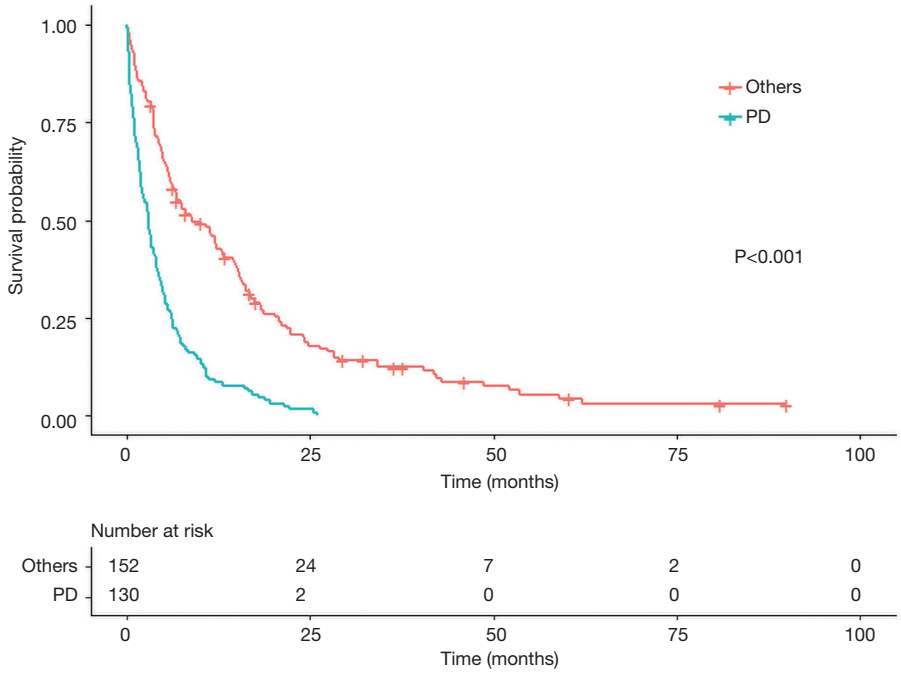


Figure 3 Overall survival of patients with PD *vs.* others. PD, extracranial disease progression; Others, extracranial disease control or newly diagnosed metastatic disease.

external validations (31,32).

Our study confirms the prognostic value of the individual components of the B-GPA (KPS, age and tumour subtype). Within tumour subtype, only the "Basal" subtype was associated with a significantly increased HR with reference to "Luminal B" (HR 1.72, 95% CI, 1.18–2.51). This ran contrary to findings from prior large population studies (9,33,34). We hypothesize that this may be because a large proportion of our population had already been heavily pre-treated and were refractory to further systemic therapy by the time of referral for radiotherapy (68.3% had targeted therapy, 81.1% had hormonal treatment, 68.4% had chemotherapy). A total of 46.1% of patients also had documented extra-cranial disease progression on treatment. Thus, the "survival benefit" conferred by subtype could have been muted. We found the number of BM to be a significant prognostic factor, which affirms its inclusion into the mB-GPA (31,32).

We have demonstrated that both B-GPA and mB-GPA are moderately successful in discriminating between OS of Asian BC patients with BM. The mB-GPA performed marginally better than the B-GPA with a lower AIC and higher C-index. Our findings echo that of an earlier European multi-centre external validation study in which the authors found a C-index of 0.64 and 0.66 for B-GPA and mB-GPA respectively (31). This is considerably lower than the adjusted C-index of 0.80 proposed during internal validation (23). A C-index of ≤0.70 lacks clinically acceptable discrimination and we suggest that additional model refinement may improve its prognostic value in BC patients with BM (35).

Extra-cranial progression has been shown in multiple studies to have a significant impact on survival and was included in several prognostic indices (6,16-18). However, this factor was excluded from analysis during initial scale creation. We agree with Sperduto *et al.* initial argument that "estimation of systemic disease is fraught with inconsistency due to the variation in type and timing of imaging studies" (15,19). However, we do not agree that factors which produce variability should be removed prematurely before careful consideration of its clinical importance. Firstly, clinical variables such as performance status, delirium and dyspnea are examples of factors that has a certain degree of subjectivity and interrater variability (36,37). Nonetheless, they remain of significant prognostic importance and their "inconsistency in assessment" does not preclude successful incorporation within useful prognostic indices (38-40). Secondly, recent efforts in the development of the

Response Evaluation Criteria in Solid Tumors (RECIST) have provided reliable and validated methods to standardise assessment of response in solid tumours (41,42). Thirdly, clinical reasoning suggests that in a patient receiving specific treatments, the disease response is a critical aspect of prognostication. Patients who demonstrate extra-cranial progression despite best efforts have limited options for further systemic therapy. These patients tend to die from uncontrolled systemic disease independent of intracranial control (24,43-45).

In our population, patients with extra-cranial progression had significantly poorer prognosis compared to the rest of the cohort (2.92 *vs*. 8.90 months) and maintained its independent prognostic value at MVA. Incorporation of extra-cranial progression as a variable improved C-index and AIC although we are aware that presence of over-fitting needs to be first verified on subsequent validation studies.

Our study has several strengths. To the best of our knowledge, this is the first validation of mB-GPA within the Asian population. We had a relatively large cohort of patients with high event rates and few losses to follow-up. There was accurate documentation of treatment received and systemic disease control.

However, our study had several limitations. Firstly, due to the retrospective nature of this study, it suffers from inherent flaws such as selection bias, missing data and reliance on the accuracy of clinical records and data captured by our institutional database. Secondly, treatment patterns captured in this historic cohort may not reflect current practice trends. A proportion of our patients declined standard of care treatment which may differ depending on centres. Thus, this limits generalizability of our results. Thirdly, our institutional database comprised of only patients with symptomatic BM referred to the Radiation Oncology Department for consideration of radiotherapy. Thus, we were unable to include patients with less symptomatic and smaller BM who underwent systemic therapy alone. Lastly, a small proportion of our patients achieved the highest GPA band of 3.5–4.0 as the patients in our study tended to be older and had poorer performance status. We were unable to adequately analyse this subgroup of patients.

Conclusions

Our results show that mB-GPA is marginally more discriminating than B-GPA and both scores display moderate abilities in stratifying survival in BC patients with BM. In addition, we strongly propose the inclusion of extra-cranial disease progression as a factor in future model development due to its significant impact on survival.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by Singhealth Central Institutional Review Board (CIRB Ref No. 2013/1037/B). Waiver of consent was granted considering the retrospective, non-interventional nature of study.

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