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Original article

External validation of Modified Breast Graded Prognostic Assessment for breast cancer patients with brain metastases: A multicentric European experience

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ABSTRACT

Background: Several prognostic scores have been developed to estimate survival of breast cancer (BC) patients with brain metastases (BM). Modified Breast Graded Prognostic Assessment (GPA), based on a single-institution cohort of 1552 patients, has been proposed as refinement of Breast-GPA. In addition to age, tumour subtype and KPS, Modified Breast-GPA comprises number of BM. This study was designed to validate Modified Breast-GPA.

Patients and methods: Clinical data of 668 BC patients diagnosed with BM at four institutions between 1996 and 2016 were reviewed. Patients were classified by Breast-GPA and Modified Breast-GPA. Overall survival (OS) was calculated from time of BM diagnosis to death or last follow-up. Cox proportional models were used to calculate hazard-ratios and their 95% CI. The performances of Breast-GPA and Modified Breast-GPA were compared using Harrell's concordance index.

Results: Median age at BM diagnosis was 56 years (range 24–85). At last follow-up, 632 patients (94.6%) had died. Median OS was 8.1 months (95% CI 6.9–9.4). The number of BM (1–3 vs. >3) was significantly associated with OS in univariate analysis ($p < 0.001$) and having >3 BM was identified as a negative prognostic factor in multivariate analysis. Both Breast-GPA and Modified Breast-GPA accurately predicted OS ($p < 0.001$ for both scores). Performance of Modified Breast-GPA was better: concordance indices were 0.6390 (95% CI, 0.6381 to 0.6399) and 0.6647 (95% CI, 0.6639 to 0.6655) for Breast-GPA and Modified Breast-GPA, respectively ($p < 0.001$).

Conclusions: This work provides the first external independent validation of Modified Breast-GPA and confirms its better performance as compared to Breast-GPA.

1. Introduction

Central nervous system (CNS) metastases are a serious complication of solid tumours, associated with functional deterioration and a poor prognosis [1]. Breast cancer (BC) is one of the most

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common causes of brain metastases (BM) [2]. Among patients with metastatic BC, approximately 10–15% will present clinically evident CNS metastases during the course of their disease [1]. BC molecular subtypes play an important role in identifying patients at increased risk of BM [3,4]: approximately 30% of Human epidermal growth factor receptor type 2 (HER2) positive and 50% of triple-negative (TN) metastatic BC patients will develop CNS metastases [5–7]. Over the last decades, a better control of systemic disease and advances in diagnostic imaging have led to an increase in BM incidence in BC patients. This is particularly evident in HER2+ BC in relation with the better systemic control that can be achieved with the use of anti-HER2 targeted treatments [5,6].

BC-related BM have been traditionally considered a late complication of progressive metastatic disease [2,8]. They are associated with poor prognosis, with reported 1-year and 2-year survival rates of 20% and 2%, respectively [1]. However, BC patients diagnosed with BM represent an extremely heterogeneous group of patients with significant differences in terms of clinical presentation and prognosis. Indeed, some patients will eventually achieve prolonged survivals from the time of BM diagnosis, while others will have a dismal prognosis [3,9,10]. The prognosis of these patients has been shown to vary depending on clinical and histopathologic factors [9,11–14]. The main prognostic factors identified are performance status and age at time of BM diagnosis, BC subtype, number of BM and the presence and status of extracranial disease (controlled vs. uncontrolled) [9,11–13].

As therapeutic options for these patients are gradually increasing, adequately predicting the outcome of patients with BC-related BM has become crucial. For this reason, prognostic scores that include independent prognostic variables have been developed in order to accurately predict patients' outcome and adapt treatments accordingly. The Graded Prognostic Assessment (GPA), originally developed from a cohort of 1960 patients with BM included in the Radiation Therapy Oncology Group (RTOG) protocols, is one of the best known prognostic scores. It has undergone subsequent refinements in the past years [9,13]. In its adapted version for BC-related BM, based on a cohort of 400 BC patients receiving radiation therapy for newly diagnosed BM, Sperduto et al. identified molecular tumour subtype, KPS and patient's age as independent prognostic factors and incorporated all of these factors in a Breast-GPA score [9]. This model was not able to identify number of BM as an independent prognostic factor, although this variable was included in the initial GPA analysis. However, given the clinical relevance of number of BM with regards to therapeutic decisions and the prognostic role identified for this variable in larger studies [10,15], a subsequent study was conducted by Subbiah et al. on a mono-institutional cohort of 1552 BC patients diagnosed with BM, and a modified version of Breast-GPA incorporating number of BM was developed [10]. In this study, Subbiah et al. showed that this new model, the Modified Breast-GPA score, performed better in predicting outcome as compared to the Breast-GPA score [10]. However, external validation in an independent cohort of BC patients diagnosed with BM is still missing.

The aim of the present analysis is to validate Modified Breast-GPA in a large multinational cohort of BC patients diagnosed with BM, and to evaluate its value as a prognostic scoring tool for survival as compared to the Breast-GPA score.

2. Patients and methods

2.1. Patients

A retrospective review of medical records was conducted in order to identify BC patients newly diagnosed with BM between September 1996 and November 2016 in four European cancer centres: Montpellier (Montpellier regional Cancer Institute) in France, Padova (Istituto Oncologico Veneto) in Italy, Nice (Center Antoine Lacassagne) in France, and Halle (Department of Gynaecology, Martin Luther University Halle-Wittenberg) in Germany.

Inclusion criteria were: histologically proven invasive BC, age >18 years at the time of BC diagnosis, intraparenchymal BM radiologically confirmed using contrast-enhanced cerebral computed tomography scan and/or magnetic resonance imaging of the brain. Patients with diagnosis of leptomeningeal carcinomatosis alone, in the absence of intraparenchymal brain metastases, were excluded. Presence of leptomeningeal disease at time or after BM diagnosis was allowed.

Clinical and biological parameters for each patient, including patients demographics, primary tumour characteristics (as histologic subtype, grade, hormone receptor (HR) status and HER2 status), and dates of diagnosis of primary BC and CNS metastases were included in a dedicated database. Estrogen receptor (ER) and progesterone receptor (PgR) expression was determined by immunohistochemistry; positivity was defined as immunohistochemistry staining in at least 1% of tumour cells. HER2 status was defined as positive in case of immunohistochemistry score 3 + and/or amplification by fluorescent in situ hybridization.

Patient were classified, according to immunohistochemistry and fluorescent in situ hybridization performed on the primary tumour, in four BC subtypes: "TN type" (HR-/HER2-), "luminal type" (HR+/HER2-); "HER2+ type" (HR-/HER2+) and "luminal-HER2+ type" (HR+/HER2+).

BM-specific data was also collected, including number of BM, KPS at the time of BM diagnosis, local and systemic treatments administered from BM diagnosis up to last follow-up.

This study was approved by the local institution ethics committees. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Considering the retrospective, non-interventional nature of this study, formal consent was not deemed necessary.

2.2. Statistical analysis

For each patient, Breast-GPA and Modified Breast-GPA scores were calculated based on previously defined criteria (Table 1) [9,10]. Each score divided patients into four groups: 0 to 1.0, 1.5 to 2.0, 2.5 to 3.0, and 3.5 to 4.0. A score of 4.0 correlated with best prognosis for both scores [9,10].

Descriptive statistics including percentages, medians and ranges were performed for patients' demographics and clinical

Table 1
Breast -graded prognostic assessment and modified breast-graded prognostic assessment scores.

Breast – Graded Prognostic Assessment 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			
Modified Breast – Graded Prognostic Assessment 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 to 3			

Prognostic categories: 0–1.0; 1.5–2.0; 2.5–3.0; 3.5–4.0.
Abbreviations: BC, breast cancer; BM, brain metastases; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; KPS, Karnofsky Performance Status; TN, triple-negative.

characteristics.

Overall survival (OS) was defined as the time interval from BM diagnosis to death from any cause. Patients alive without event at cut-off date of this analysis (January 31st, 2017) were censored at date of last follow-up. Median OS was estimated using the Kaplan–Meier method and reported with 95% confidence intervals (95% CIs). Kaplan–Meier curves were used to present OS for patients in each group. The log-rank test was used to compare OS between groups. Univariate and multivariate Cox regression modelling for proportional hazards was used to calculate hazard-ratios and their 95% CI. All reported p values were two-sided, and significance level was set at 5% ($p < 0.05$).

Harrell's concordance Index (C index) was used to assess the discriminating ability (ability of model to separate patients with different outcomes) of the two prognostic scores.

Analyses were performed using IBM SPSS (version 24), except for analysis related to C index, which were performed using compare C package of R software, version 3.3.3 [16].

3. Results

3.1. Patient characteristics

Overall, we identified 668 BC patients with BM meeting inclusion criteria, which were all included in the analysis. Table 2 summarizes patient and tumour characteristics.

The median age at BC diagnosis was 50 years (range 22–82). Most patients were diagnosed with invasive ductal ($N = 554$, 83.1%) and with histological grade 3 tumours ($N = 365$, 54.6%). Overall, 162 patients (24.3%) were categorized as TN, 206 (30.8%) as HR+/HER2-, 144 (21.6%) as HR-/HER2+ and 136 (20.4%) as HR+/HER2+.

The median age at BM diagnosis was 56 years (range 24–85). Almost a quarter of included patients ($N = 164$, 24.6%) presented with a single BM, while another half ($N = 355$, 53.1%) had more than three BM. Information on KPS at the time of BM diagnosis was available for 639 out of 668 patients (95.7%): most patients had a KPS ≥70 ($N = 438$, 65.6%) (Table 2).

The majority of patients received at least one treatment modality, local or systemic, while only 80 patients (12%) were treated with best supportive care alone (Table 2). More than half of the patients ($N = 384$, 57.5%,) received multimodality treatment for brain metastases (combination of radiotherapy, neurosurgery and systemic therapy). Treatments received by patients after BM diagnosis are further detailed in Supplementary Table 1. 149 patients did not receive any local treatment for CNS disease (neurosurgery or radiotherapy). Characteristics of these patients are summarized in Supplementary Table 2.

30 patients (4.5%) presented leptomeningeal disease at time of BM diagnosis. Clinical characteristics of these patients are summarized in Supplementary Table 3.

Table 2
Patient and tumour characteristics at time of brain metastases diagnosis.

		Median	Range
Age at BC diagnosis, years		50	22–82
Age at BM diagnosis, years		56	24–85
		N. of patients	%
Age at BM diagnosis	≤50 years	232	34.7%
	>50 years	436	65.3%
Tumour histology	Ductal	554	83.1%
	Lobular	55	8.2%
	Other histology	58	8.7%
	NA	1	0.1%
Grade	G1-G2	252	37.7%
	G3	365	54.6%
	NA	51	7.6%
Sex	Female	667	99.9%
	Male	1	0.1%
Molecular subtype	TN	162	24.3%
	HR+/HER2-	206	30.8%
	HR-/HER2+	144	21.6%
	HR+/HER2+	136	20.4%
	NA	20	3.0%
Karnofsky Performance Status	90 to 100	125	18.7%
	70 to 80	313	46.9%
	60	82	12.3%
	≤50	119	17.8%
	NA	29	4.3%
Number of BM	1	164	24.6%
	2	97	14.5%
	3	50	7.5%
	>3	355	53.1%
	NA	2	0.3%
Leptomeningeal disease	No	638	95.5%
	Yes	30	4.5%
Breast-GPA	3.5–4	86	12.9%
	2.5–3	240	35.9%
	1.5–2	187	28.0%
	0–1	107	16.0%
	NA	48	71.9%
Modified Breast-GPA	3.5–4	37	5.5%
	2.5–3	205	30.7%
	1.5–2	249	37.3%
	0–1	128	19.2%
	NA	49	7.3%
Treatment: Radiotherapy	WBRT	451	67.5%
	SRS	48	7.2%
	Other CNS radiotherapy	35	5.2%
	No radiotherapy	158	23.7%
Treatment: Surgical resection	Yes	71	10.6%
	No	597	89.4%
Treatment: Systemic CT	Yes	436	65.3%
	No	227	34.0%
	NA	5	0.7%
Treatment: Targeted Therapy	Yes	216	32.3%
	No	448	67.1%
	NA	4	0.6%

Abbreviations: BC, breast cancer; BM, brain metastases; CNS, central nervous system; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; *N*., number; NA, not available; SRS, stereotactic radiosurgery; TN, triple-negative; WBRT, whole-brain radiotherapy

3.2. Prognostic factors for OS after BM diagnosis

At last follow-up, 632 patients (94.6%) had died. Median OS was 8.1 months (95% CI 6.9–9.4). The impact of several known prognostic factors on OS from BM diagnosis was investigated using univariate Cox regression modelling (Table 3). As expected, primary tumour subtype, age and KPS at the time of BM diagnosis were all significantly associated with OS from BM diagnosis in univariate analysis (Table 3). The number of BM (1–3 BM vs. >3) was also a significant prognostic factor in the univariate model ($p < 0.001$). The multivariate model confirmed the independent negative prognostic value of having >3 BM at diagnosis (HR 1.31, 95% CI 1.11–1.55), thus supporting its inclusion in the prognostic score. Presence of leptomeningeal disease also was a significant negative prognostic factor, both in the univariate ($p < 0.001$) and in the multivariate model (HR 2.61, 95% 1.71–3.97).

3.3. Breast-GPA and Modified Breast-GPA: validation and comparison of performances

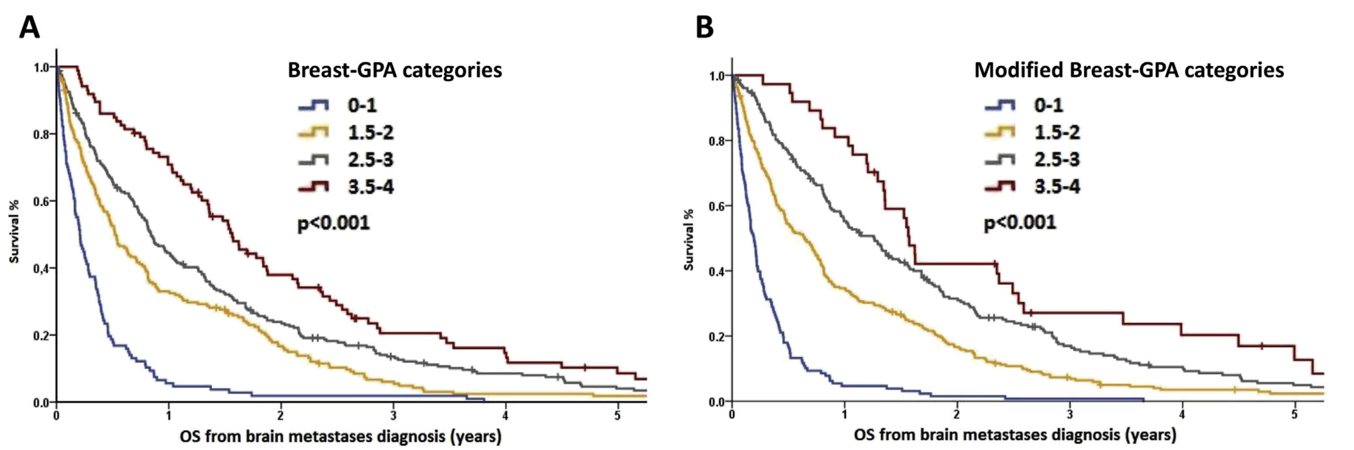
Breast-GPA and Modified Breast-GPA were calculated for all patients for whom data for relevant variables was available (620 and 619 patients, respectively) (Table 2).

Both scores predicted OS from BM diagnosis (Fig. 1A, Fig. 1B). Median OS was 2.5, 6.3, 10.1, and 18.8 months for patients with a

Table 3
Univariate and multivariate Cox Proportional Hazards Model for overall survival (OS).

		Median OS months (95% CI)	Univariate Hazard Ratio (95%CI)	Univariate *p*	Multivariate Hazard Ratio (95%CI)
BC subtype	TN	4.9 (3.9–6.0)	1.60 (1.26–2.3)	**<0.001**	1.55 (1.21–1.98)
	HR+/HER2-	6.2 (4.2–8.1)	1.34 (1.07–1.67)		1.29 (1.03–1.63)
	HR-/HER2+	9.9 (7.1–12.8)	1.02 (0.8–1.30)		0.93 (0.72–1.20)
	HR+/HER2+	12.9 (9.7–16.0)	ref		ref
Age at BM diagnosis	≤50 years	12.1 (9.5–14.7)	ref	**<0.001**	ref
	>50 years	5.8 (4.6–7.1)	1.48 (1.25–1.74)		1.39 (1.17–1.65)
KPS	90 to 100	16.3 (13.5–19.1)	ref	**<0.001**	ref
	70 to 80	10.6 (9.0–12.2)	1.43 (1.15–1.78)		1.43 (1.14–1.79)
	60	4.7 (2.9–6.6)	2.76 (2.05–3.71)		2.79 (2.06–3.79)
	≤50	1.9 (1.6–2.2)	6.25 (4.75–8.21)		5.48 (4.11–7.31)
Number of BM	1–3	9.9 (7.9–11.9)	ref	**<0.001**	ref
	>3	6.2 (4.7–7.6)	1.38 (1.18–1.62)		1.35 (1.14–1.59)
Leptomeningeal disease	No	8.5 (7.4–9.7)	ref	**<0.001**	ref
	Yes	2.9 (1.6–4.1)	2.04 (1.40–2.97)		2.61 (1.71–3.97)

Abbreviations: BC, breast cancer; BM, brain metastases; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; KPS, Karnofsky Performance Status; TN, triple-negative.



Breast-GPA category	N. of patients (%)	Median OS, months (95% CI)	Hazard Ratio (95% CI)	*p*
0-1.0	107 (17.3%)	2.5 (1.8-3.2)	4.90(3.62-6.64)	**<0.001**
1.5-2	187 (30.2%)	6.3 (4.9-7.7)	2.00(1.53-2.61)	
2.5-3	240 (38.7%)	10.1 (8.6-11.6)	1.46(1.13-1.90)	
3.5-4	86 (13.9%)	18.8 (14.9-22.6)	ref	

Modified Breast-GPA category	N. of patients (%)	Median OS, months (95% CI)	Hazard Ratio (95% CI)	*p*
0-1.0	128 (20.7%)	2.3 (1.8-2.8)	6.84 (4.59-10.20)	**<0.001**
1.5-2	249 (40.2%)	7.7 (5.9-9.6)	2.29(1.58-3.33)	
2.5-3	205 (33.1%)	15.2 (12.1-18.2)	1.44(0.99-2.09)	
3.5-4	37 (6.0%)	18.9 (17.2-20.5)	ref	

Fig. 1. Kaplan-Meier overall survival (OS) curves, median OS in months and hazard ratio according to Breast-GPA (A) and Modified Breast-GPA (B) categories in our validation cohort. Percentages are relative to the total number (N.) of patients with available score.

Breast-GPA score of 0–1.0, 1.5 to 2.0, 2.5 to 3.0, and 3.5 to 4.0, respectively ($p < 0.001$) (Fig. 1A). Median OS was 2.3, 7.7, 15.2, and 18.9 months for patients with a Modified Breast-GPA score of 0–1.0, 1.5 to 2.0, 2.5 to 3.0, and 3.5 to 4.0, respectively ($p < 0.001$) (Fig. 1B).

Concordance indices were 0.6390 (95% CI 0.6381 to 0.6399) and 0.6647 (95% CI 0.6639 to 0.6655) for Breast-GPA and Modified Breast-GPA, respectively ($p < 0.001$).

4. Discussion

This study was conducted with the aim of confirming the prognostic value of number of BM and validating the use of Modified Breast-GPA as a tool for predicting survival [10].

It included a large multinational cohort of BC patients diagnosed with BM that showed clinical and biological features consistent with previous studies: most patients had high-grade tumours (54.6%) and the proportions of patients with HER2-positive (41.9%) and TN (24.3%) tumours were higher than in a general population of metastatic BC patients not selected for BM [10,17–20]. KPS at the time of BM diagnosis also showed a distribution similar to that described in previous studies [9,10], with most patients (65.6%) presenting a KPS≥70. Interestingly, our cohort of patients was older than that described by Subbiah et al., with most patients aged >50 years at the time of BM diagnosis [10]. This difference might be explained by the fact that the Modified Breast-GPA was developed in a mono-institutional cohort of patients from a large cancer center, thus possibly selectively attracting younger patients.

Even in this slightly different clinical setting, our results clearly confirm the prognostic value of number of BM ($p < 0.001$), both in a univariate and multivariate model. This is not unexpected, as number of BM represents one of the most relevant variables in defining clinical management of BC patients with CNS involvement. In fact, advances in systemic therapy, with increased availability of agents with activity on the CNS, have contributed to gradually increase survival of BC patients diagnosed with BM in the last decades. This has progressively reduced the role of whole-brain radiotherapy in the treatment of single or oligo BM in favour of more focalized and less toxic local treatments, such as stereotactic radiosurgery [22]. In this context, we might expect a progressive increase over time in the prognostic importance of the number of BM as a numeric benchmark of three/four brain lesions is commonly used to define the applicability of localized treatments as compared to classical whole-brain radiotherapy [21].

In addition, the cohort of BC patients originally used by Sperduto et al. to define Breast-GPA was significantly smaller than both the Modified Breast-GPA and our cohort. Thus, the inability of the Breast-GPA study to identify number of BM as an independent prognostic factor may be partly attributed to the limited number of patients included [9,10].

Patients with leptomeningeal involvement at time of BM diagnosis had poorer prognosis (median OS 2.9 months) and leptomeningeal disease maintained its independent negative prognostic value at multivariate analysis. With this in mind, presence of leptomeningeal disease should be thoroughly investigated in BC patients diagnosed with BM and its prognostic impact should be kept into account.

By internal guidelines of all four institutions involved, radiological evaluation of the CNS was only performed in symptomatic BC patients and scheduled serial CT scans were not used. However, due to the retrospective and multicentric nature of this study, we cannot exclude that some differences might be present in radiological follow-up of BC patients according to tumour subtype. In fact, clinicians might have been more prone to perform CNS radiological evaluations in patients with HER2+ and TN disease thus possibly diagnosing some patients with very limited asymptomatic brain metastases, whereas CNS involvement in HR + BC patients might have been diagnosed at more advanced stages.

Even with these limitations, this analysis represents, to our best knowledge, the first validation of Modified Breast-GPA [10] in an external cohort, confirming its prognostic value for OS from BM diagnosis in a separate multinational cohort of BC patients ($p < 0.001$). When compared to Breast-GPA [9], Modified Breast-GPA performed better in predicting prognosis of BC patients with BM ($p < 0.001$). These results prompt its use in both clinical practice and clinical trials.

Prognostic scores for BC patients with CNS metastases have been progressively ameliorated over last two decades, reflecting the clinical need for an increasingly accurate prediction of patient outcome in order to adapt treatment strategies accordingly. On the other hand, the progressive evolution of these scores mirrors the changing scenario of BC-related BM. In this clinical setting, recent advances in systemic therapies and in radiation therapy techniques have substantially modified and improved survival from BM diagnosis, at least for some subgroups of patients [3,10]. Consequently, prognostic factors for BC patients diagnosed with BM have changed over time under the modulating effect of effective treatment (e.g. anti-HER2 targeted therapy). Continuous reassessment and amelioration of prognostic tools is thus necessary.

In summary, our results highlight the prognostic role of number of BM in BC patients, thus supporting the addition of this variable to prognostic scores. Modified Breast-GPA integrates number of BM, age and KPS at the time of BM diagnosis, and BC subtype, therefore providing a prognostic tool including four simple and highly relevant patient characteristics. External validation of Modified Breast-GPA and its ameliorated performance in predicting prognosis of these patients as compared to Breast-GPA score prompt its use both as prognostic tool to guide management of patients with BC-related BM in clinical practice and as patient selection tool for prospective clinical trials.

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None declared.

Conflict of interest statement

None declared.

Ethical approval

The study was approved by the local institution ethics committees. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Considering the retrospective, non-interventional nature of this study, formal consent was not deemed necessary.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.breast.2017.10.006.

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