Comparison of Breast Graded Prognostic Assessment Scores in a Turkish Cohort of Patients with Brain Metastatic Breast Cancer

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ABSTRACT

Breast Graded Prognostic Assessment (B-GPA), modified B-GPA (mB-GPA), and updated B-GPA (uB-GPA) are the best-known prognostic tools used to stratify survival in patients with brain metastatic breast cancer. However, clinically important variables, such as extracranial disease (ECD) status, was not included in these models. We aimed to evaluate the utility of these three prognostic tools in a Turkish cohort and investigate the prognostic value of ECD status. Data from breast cancer (BC) patients diagnosed with brain metastasis (BM) between January 2012 and December 2022 were collected retrospectively. Patients were classified according to B-GPA, mB-GPA, and uB-GPA scores. Univariate and multivariate analyses were performed using the Cox proportional hazards model to investigate prognostic factors for overall survival (OS). The Kaplan-Meier method was used to estimate OS, and the log-rank test was used to compare survival between scores. B-GPA, mB-GPA, and uB-GPA performances were compared using Harrell's concordance index. In our cohort of 199 patients, B-GPA, mB-GPA, and uB-GPA were confirmed to be useful prognostic tools for OS and showed excellent discrimination between survival curves ($p< 0.001$). We found that the uB-GPA's C-index of 0.689 significantly better predicted OS than the other two tools. ECD status was shown to be an important predictor of OS in univariate and multivariate analyses ($p< 0.001$). Including ECD status as a factor in the uB-GPA test increased the C-index to 0.709 (log-rank $p< 0.0001$). ECD status provides independent prognostic information beyond the prognostic scores commonly used in BCBM.

Keywords: Breast cancer, Brain metastasis, Survival outcomes, Prognostic index, Updated B-GPA

INTRODUCTION

Breast cancer (BC) is the second most common cause of brain metastases (BMs), which are diagnosed ten times more frequently than primary brain tumors.[1] Between 15-35% of BC patients develop BM during the disease course.[2] BMs usually occur in the late stage of metastatic BC (mBC) after various systemic treatments, with an average appearance time of 33 months. However, in some cases, the brain may be the site of initial relapse.[3]

Advances in early diagnosis and effective targeted therapies have increased the survival rate in BC patients, which has led to a rise in BM incidence over the past 20 years due to better survival rates, routine follow-up imaging, and improved imaging technology.[4] BMs in BC are heterogeneous, with median overall survival (OS) ranging from 4 to 25 months.[5] Risk factors affecting survival include age, Karnofsky performance status (KPS), tumor histology, BM count, local or systemic treatment, and extracranial disease (ECD) control.[6,7] Various prognostic indices have been developed based on these variables.[8-13]

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Historically, patients with BM had a poor prognosis, and individualized treatment was often overlooked. In the late 1990s, the Radiation Therapy Oncology Group (RTOG) developed the 'Recursive Partitioning Analysis' (RPA), classifying patients by prognosis. OS was 7.1 months for the best prognostic score (RPA class 7) and 2.3 months for the worst (RPA class 3).[14]

In 2008, Sperduto et al. introduced the 'Graded Prognostic Assessment (GPA)' based on age, KPS, and tumor subtype, which was less subjective and easier to use than RPA. Notably, 'extracranial disease status' was not included due to lack of standardization in clinical and radiological evaluation.[15]

In 2010, Sperduto et al. found OS varied significantly with diagnosis-specific prognostic factors, leading to the development of diagnosis-specific GPA (DS-GPA) and breast cancer-specific GPA (B-GPA). Interestingly, BM count was excluded as a significant factor, and median OS of 25.3 months for the best B-GPA score and 3.4 months for the worst.[16,17]

In 2015, Subbiah et al. confirmed B-GPA as a prognostic tool for OS in a cohort of 1552 patients. Determining that BM count was an independent risk factor for OS, they integrated it into B-GPA as a fourth variable and developed a modified B-GPA (mB-GPA).[18] Finally, in 2020, Sperduto et al. updated this score by incorporating extracranial metastasis (ECM) into the uB-GPA, demonstrating that the median survival time for the poor prognostic group is approximately 6 months, whereas the best prognostic group exhibits survival exceeding 3 years.[19]

The aim of this study is to validate the survival predictions of three prognostic tools in patients with BMBC and to evaluate ECD control as an independent prognostic factor. Conducted within the Turkish BMBC population, this study will contribute uniquely to the literature by enabling comparisons of the effectiveness of these prognostic tools across different populations and optimizing their clinical use. Additionally, it will guide more targeted, evidence-based treatment planning by classifying patients according to their prognosis.

PATIENTS AND METHODS

Patient Selection and Data Collection

All BC patients with biopsy-proven BM diagnosed at Trakya University Hospital, Medical Oncology clinic, between January 1, 2012, and December 31, 2022, were selected as the research cohort. Patients aged 18 years and older with BM confirmed by contrast-enhanced cranial computed tomography and/or cranial magnetic resonance imaging, and possessing the essential prognostic factors required for GPA testing, such as age, KPS, tumor molecular subtype, and ECD status, and, for HER2-positive patients, having received trastuzumab therapy were included in the study. Patients with missing data or recurrent BM were excluded.

Information such as age, tumor subtype, KPS, BM count and size, presence of leptomeningeal involvement, ECD status, number of metastatic sites (NoMS), treatment, and other patient characteristics were collected retrospectively from the Medical Oncology Unit archive database. Hormone receptor status (HR) was determined by immunohistochemistry (IHC); positivity was defined as staining in at least 1% of tumor cells. Human Epidermal Growth Factor Receptor 2 (HER2) status was assessed by IHC, and for tumors scored +3 or +2 by IHC, a FISH test was performed; tumors with amplified HER2 gene were considered HER2+. Patients were divided into four BC subtypes: 'Luminal A' (HR+, HER2-), 'Luminal B' (HR+, HER2+), HER2-enriched (HR-, HER2+), and 'Basal-like' (HR-/HER2-). B-GPA, mB-GPA, and uB-GPA scores were calculated for each patient according to published criteria (See Table 1). Patients were classified into four groups within each of the three prognostic indices (0-1.0, 1.5-2.0, 2.5-3.0, and 3.5-4.0). This scoring system categorizes patients to represent the worst prognosis for scores between 0–1 and the best prognostic group for scores between 3.5–4. Additionally, these calculations can be performed using the free online platform available at https://brainmetgpa.com/, which also provides an estimated survival time, offering valuable support for clinical decision-making.

Overall survival was defined as the time from the date of BM diagnosis to the date of death or, for

Table 1. Comparison of prognostic factors and scoring criteria in different graded prognostic assessment models (B-GPA, mB-GPA, uB-GPA)

B-GPA					
Factor	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Age	≥ 60	< 60	-	-	-
KPS	≤ 50	60	70-80	90-100	-
Subtype	Basal like	-	Luminal A	HER2 enriched	Luminal B
mB-GPA					
Factor	0	0.5	1.0	1.5	2.0
Age	> 50	≤ 50	-	-	-
KPS	≤ 50	60	70-80	90-100	-
Subtype	Basal like	Luminal A	Luminal B	HER2 enriched	-
No of BM	> 3	≤ 3	-	-	-
uB-GPA					
Factor	0	0.5	1.0	1.5	2.0
Age	≥ 60	< 60			-
KPS	≤ 60	70-80	90-100	-	-
Subtype	Basal like	Luminal A	-	HER2, Luminal B	-
No of BM	> 1	1	-	-	-
ECM	Present	Absent	-	-	-

Abbreviation, KPS; Karnofsky erformance status, B-GPA; Breast Graded Prognostic Assessment, mB-GPA; Modified Breast Graded Prognostic Assessment, uB-GPA; Updated Breast Graded Prognostic Assessment

patients still alive, to the date of last follow-up. BM count and NoMS were determined based on the evaluation of available imaging or radiological reports. Patients were also grouped according to ECD control. Patients showing complete, partial, or stable response during systemic treatment were called 'ECD control,' while those with progressive disease were called 'ECD progression.' ECD status was determined based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria and/or physician assessment documented in clinical notes.

This study was approved by the Trakya University Ethics Committee (2023/363; October 9, 2023) and conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

All analyses were performed using the SPSS and MedCalc statistical software packages (IBM SPSS Statistics for Windows, Version 27.0. Armonk, N.Y., USA, and MedCalc Statistical Software Ltd. Ostend, Belgium; https://www.medcalc.org. Descriptive statistics were performed for the demographic and clinical characteristics of the patients. Univariate and subsequently multivariate Cox regression analyses were used to investigate prognostic factors that may affect OS in the study cohort. Harrell's concordance index (C-index) was used to evaluate the discriminative ability of the B-GPA, mB-GPA, and uB-GPA prognostic models. OS was calculated using the Kaplan-Meier method and is reported with a 95% confidence interval (95% CI). The log-rank test was used to compare OS between groups. All reported p-values were two-sided, and the significance level was set at 5% ($p < 0.05$).

RESULTS

Clinical Features

A total of 199 patients (6 males, 3%) were included in this study. The characteristics of the cohort are presented in Table 2. At the time of BM diagnosis, the median age of the patients was 55 years (range 26-82). The median time from BC diagnosis to BM development was 31 months (range 0-247 months). The time to BM development was shorter in the basal-like subtype compared to HER2-enriched, Luminal B, and Luminal A subtypes (20 months vs. 26 months, 31 months, and 46 months, respectively).

At the time of BM diagnosis, the majority of patients had a KPS score above 70 (n= 146, 73.3%)

Table 2. Characteristics and treatment details of patients with brain metastatic breast cancer

		Median (min-max)	
Median age at mBC		54 (26-80)	
Median age at BMBC		55 (26-82)	
		Median (95%CI)	
Median survival after mBC (months)		28.1 (26.7-36.7)	
Median survival after BMBC (months)		9.9 (6.4-13.3)	
		Number of patients	**%**
Sex	Female	193	97.0
	Male	6	3.0
Age at BM diagnosis	< 55 years	96	48.2
	≥ 55 years	103	51.8
Sites of metastasis at BM development	Only BM	39	19.6
	BM+Bone	36	18.1
	BM+Visceral	33	16.6
	BM+Bone+Visceral	91	45.7
Number of metastatic sites	1	39	19.6
	2	56	28.1
	3	50	25.1
	4	17	37
	≥ 5	8.5	18.9
Tumor histology	Ductal	167	83.9
	Lobular	11	5.5
	Other	17	8.5
	NA	4	2.0
Grade	G1-2	81	40.7
	G3	92	46.2
	NA	26	13.1
Hormone receptor	Positive	110	55.3
	Negative	89	44.7
Molecular subtype	Luminal A	67	33.7
	Luminal B	43	21.6
	Her2 enriched	50	25.1
	Basal like	39	19.6
Karnofsky Performance Status	90-100	50	25.1
	70-80	96	48.2
	60	40	20.1
	< 50	13	6.5
Number of BM	1	62	31.2
	2	52	26.1
	3	25	12.6
	> 3	60	30.2
Largest brain metastasis diameter	0-3 cm	146	73.4
	3-5 cm	37	18.6
	> 5 cm	16	8.0
Leptomeningeal disease	No	170	85.4
	Yes	29	14.6
Disease status	Extra-cranial disease progression	96	48.2
	Extra-cranial disease control	103	51.8
Breast-GPA	3.5-4	37	18.6
	2.5-3	92	46.2
	1.5-2	48	24.1
	0-1	22	11.1
Modified B-GPA	3.5-4	20	10.1
	2.5-3	83	41.7
	1.5-2	72	36.2
	0-1	24	12.1
Updated B-GPA	3.5-4	19	9.5
	2.5-3	84	42.2
	1.5-2	70	35.2
	0-1	26	13.1

Continued

Table 2. Characteristics and treatment details of patients with brain metastatic breast cancer (***Continued***)

		Median (min-max)	
Treatment: Radiotherapy	WBRT	131	65.8
	Surgery±WBRT	34	17.1
	Other	13	6.5
	No-RT	21	10.6
Treatment: Surgical resection	No	73	36.7
	Yes	126	63.3
Treatment: Hormone treatment received	No	96	48.2
	Yes	103	51.8
Treatment: Target treatment received	No	108	54.3
	Yes	91	45.7

Abbreviation, BM; Brain metastasis, G; Grade, B-GPA; Breast Graded Prognostic Assessment, WBRT; Whole brain radiation therapy

Table 3. Univariate and Multivariate Cox Regression analysis of prognostic factors for overall survival in brain metastatic breast cancer patients

	Median OS, months (95% CI)	Univariate Cox Hazard ratio (95% CI)	p	Multivariate Cox Hazard ratio	p
Age at BM					
< 55 years	13.4 (7.0-20.0)	Ref. 0.68 (0.50-0.92)	0.014	0.78 (0.51-1.2) Ref.	0.26
≥ 55 years	7.6 (4.3-11.0)				
Karnofsky performance status					
90-100	29.3 (19.1-39.5)	Ref.	< 0.001	Ref.	
70-80	11.9 (9.3-14.5)	0.03 (0.01-0.07)		0.04 (0.02-0.09)	< 0.001
60-70	3.0 (2.7-3.2)	0.06 (0.03-0.13)		0.07 (0.04-0.15)	
< 50	1.3 (1.0-1.58)	0.2 (0.10-0.41)		0.21 (0.11-0.44)	
HR status					
Positive	12.6 (9.0-16.3)	Ref.			
Negative	8.5 (4.3-12.6)	1.17 (0.89-1.58)	0.30	–	
Molecular subtype					
Her2 enriched	14.7 (5.0-24.4)	Ref.			
Luminal B	12.9 (6.9-18.9)	0.88 (0.56-1.38)	0.073	–	
Luminal A	10.4 (5.5-15.1)	1.17 (0.79-1.73)			
Basal like	5.4 (3.4-7.3)	1.60 (1.02-2.49)			
Number of brain metastases					
1-3	13.2 (7.5-18.9)	0.52 (0.38-0.70)	0.001	0.82 (0.48-1.17)	0.18
≥4	4.9 (1.8-8.1)	Ref.		Ref.	
BM diameter					
0-3 cm	11.4 (6.9-15.8)	0.87 (0.62-1.22)	0.43	–	
≥ 4 cm	9.0 (5.9-12.1)	Ref.			
Leptomeningeal metastasis					
No	3.1 (2.6-4.1)	0.41 (0.27-.0.63)	< 0.001	0.07 (0.45-0.92)	0.02
Yes	11.9 (7.9-15.9)	Ref		Ref.	
Visceral metastasis					
No	18.5 (13.4-23.6)	0.47 (0.34-0.65)	< 0.001	0.83 (0.51-1.34)	0.45
Yes	6.8 (4.2-9.2)	Ref.		Ref.	
Number of metastatic sites					
1-4	13.4 (8.7-18.1)	0.29 (0.20-.43)	< 0.001	0.50 (0.39-0.78)	<0.05
≥ 5	3.1 (2.9-3.2)	Ref.		Ref.	
ECD control					
No	20.4 (17.9-23.5)	3.08 (2.23-4.23)	< 0.001	1.73 (1.18-2.55)	<0.05
Yes	4.1 (2.4- 5.37)	Ref.		Ref.	

BM= Brain metastasis, HT= Hormone receptor, ECD= Extra-cranial disease, B-GPA= Breast Graded Prognostic Assessment

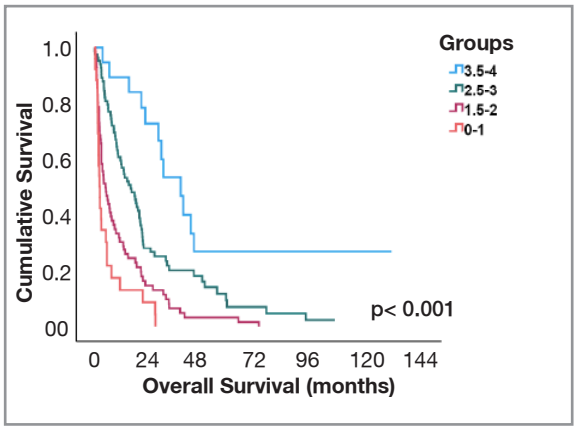

Figure 1. Kaplan-Meier overall survival curve in brain metastatic breast cancer stratified by uB-GPA scores

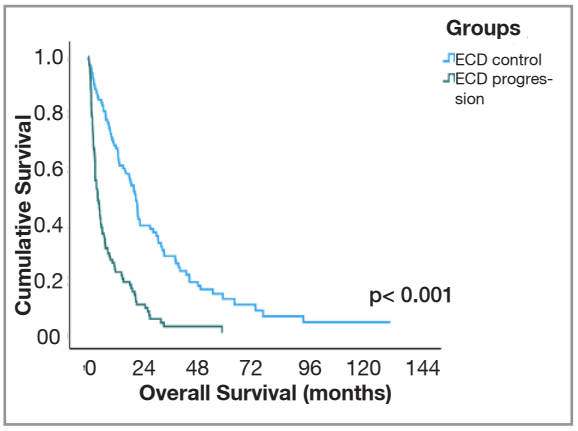

Figure 2. Kaplan-Meier overall survival curve in brain metastatic breast cancer stratified by ECD status

and 19.6% (n= 39) had only BM. Approximately one-third of the patients had >3 brain lesions, while 14.6% (n= 29) had leptomeningeal involvement. There was no significant difference in the number of brain lesions according to tumor subtype (p= 0.17), but patients with grade 3 tumors had significantly more brain lesions (p= 0.013).

The most common ECM sites were bone (n= 126, 63.3%), liver (n= 91, 45.7%), and lung (n= 82, 41.2%). A total of 18.6% (n= 37) of the patients had >5 metastatic sites, including the brain. Most patients had ECD (n= 160, 81.4%), but 51.8% (n= 103) did not have ECD progression at the time of BM diagnosis. Patients with ECD progression had significantly lower KPS scores (p< 0.05).

At the time of BM diagnosis, the majority of patients were treated with at least one local or systemic treatment modality, while only 10.6% (n= 21) received the best supportive care alone. At the time of analysis, 87.4% (n= 174) of the patients had died, with 10.3% (n= 18) occurring within the first month after BM diagnosis.

U*nivariate and Multivariate Cox Regression Analysis and Survival Analysis of Prognostic Factors*

As of December 31, 2022, when the data was recorded, 12.6% (n= 25) of the 199 patients were still alive. The median follow-up time was 28 months, and the median OS from the time of BM diagnosis was 9.9 months (95% CI: 6.4-13.3). The relationship between various known prognostic factors and OS following BM diagnosis was investigated using univariate Cox regression analysis (See Table 3). Age, KPS, number of brain metastases, leptomeningeal metastasis, visceral metastasis, number of metastatic sites and all three prognostic tools tested were significantly associated with OS, as expected. Although not statistically significant, there was a numerically notable relationship between the histological subtype of the tumor and OS. Additionally, we found that ECD status was significantly associated with OS.

Upon evaluation of the risk factors associated with OS in the univariate analysis through multivariate analysis, KPS, leptomeningeal metastasis, ECD status, and the number of metastatic sites were found to retain their independent prognostic value.

The study cohort was grouped according to B-GPA, mB-GPA, and uB-GPA scores, and the Kaplan-Meier curve for OS showed excellent discrimination between GPA bands across all prognostic tools.

B-GPA

Patients were divided into four groups according to their B-GPA score. The median OS for patients in the 0.0-1.0 band was 2.2 months (95% CI: 1.5-2.8), while for the 1.5-2.0, 2.5-3.0, and 3.5-4.0 bands, the median OS was 3.9 months (95% CI: 1.8-6.2), 12.8 months (95% CI: 8.0-17.7), and 22.2 months (95%

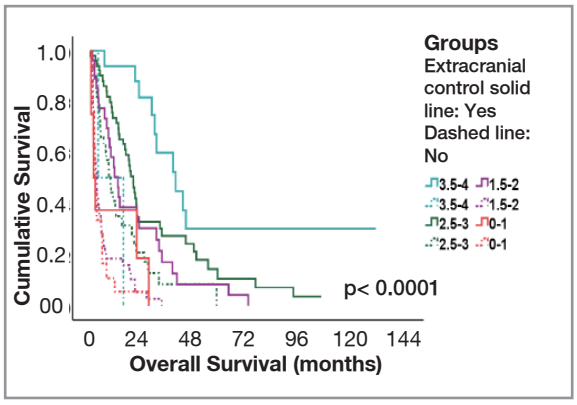

Figure 3. Kaplan-Meier overall survival curve in brain metastatic breast cancer stratified by ECD Control and uB-GPA Scores

CI: 16.4-27.9), respectively (log-rank p<0.001). The C-index, which shows the predictive power of the model, was 0.657 (95% CI: 0.551-0.764).

mB-GPA

The median OS between the four bands of the mB-GPA score was shown to be 2.0 months (95% CI: 1.5-2.5), 7.6 months (95% CI: 4.1-10.9), 16.2 months (95% CI: 10.0-22.3), and 22.2 months (95% CI: 13.9-30.5), respectively (log-rank p< 0.001), from the lowest band score. The C-index was 0.682 (95% CI: 0.568-0.796).

uB-GPA

The median OS between the four bands of the uB-GPA score was 2.2 months (95% CI: 1.5-2.8), 4.8 months (95% CI: 2.3-7.3), 15.8 months (95% CI 10.8-20.9), and 37.7 months (95% CI: 26.1-49.4), respectively (log-rank p< 0.001), from the lowest band score. Only 9.5% (n= 19) of the patients were in the best prognostic group. The uB-GPA showed a slightly better distinction and had a higher predictive power than the other two tools: C-index 0.689 (95% CI: 0.582-0.797) (See Figure 1).

Extracranial Disease Status

ECD has been shown to be an important determinant of OS. Based on ECD status, the median OS of patients with ECD progression was significantly lower at 4.1 months, whereas it was 20.4 months in the group with controlled ECD (95% CI: 1.8-8.1, log-rank p< 0.001). Multivariate analysis was performed to evaluate whether the ECD status added independent information to each of the three prognostic tools. ECD progression retained its independent prognostic value after adjustment for each of the validated prognostic tools (HR 2.91 for B-GPA, 95% CI: 2.08-4.06, p< 0.0001, HR 3.10 for mB-GPA, 95% CI: 2.22-4.32, p< 0.0001, and HR 2.45 for uB-GPA, 95% CI: 1.76-3.24, p< 0.0001). Including ECD status as a factor in the uB-GPA test increased the C-index to 0.709, (log-rank p< 0.0001). Figure 2 shows the OS curve according to the ECD status, and Figure 3 shows a representative OS curve with the addition of ECD status to the uB-GPA test.

DISCUSSION

Breast cancer, with its diverse genotypic and phenotypic profiles, presents varying prognoses among subgroups.[20] The prognosis of mBC is poor, and brain metastases are among the worst prognosis sites.[21] Current evidence-based guidelines emphasize individualizing treatment based on patient prognosis.[22-24] For patients with good prognosis, primary treatments include surgery, stereotactic radiosurgery (SRS), and whole brain radiation therapy (WBRT). For patients with poor prognosis, OS is determined by the progression and extent of ECD rather than the success of controlling brain metastases, making short-course WBRT or best supportive care (BSC) more appropriate.[23,24] The clinical benefit of WBRT in poor prognosis patients is not well defined, and its toxicity should not be overlooked.[25,26] An early British study found that 12 Gy WBRT in 2 daily fractions was as effective as longer regimens for symptomatic brain metastases patients with poor survival.[27]

In our series, 18 (10.3%) patients had a survival of ≤ 1 month, and half were treated with BSC. These patients had poor performance status (KPS≤ 70), with most showing ECD progression (n= 14) and extended disease (n= 12). Clinicians need to identify patient subgroups whose prognosis can be maintained with BSC. Retrospective data analysis has led to the development of different prognostic indices to classify patients with good and poor prognosis.[8-13] The most well-known of these indices is the B-GPA, updated in 2020.[19]

In our 10-year series, we determined that the B-GPA, mB-GPA, and uB-GPA tests were moderately successful in predicting survival in the Turkish population with BCBM. Our findings are consistent with previous limited validation studies[28-31] and the original uB-GPA results.[19] For the reliability of Harrell's C-index, A value of 0.5 indicates that the model is making random predictions, while a value of 1.0 indicates perfect discriminatory power. Generally, C-index values above 0.7 are considered to indicate good discriminatory power, values between 0.6 and 0.7 indicate moderate discriminatory power, and values below 0.6 indicate poor discriminatory power.[32] In our study, all three GPA tests were moderately successful and indicated the need for further model refinement. The median follow-up time in our series was 28 months, and the median survival was 9.9 months. For patients with B-GPA scores of 0-1.0, 1.5-2.0, 2.5-3.0, and 3.5-4.0, OS was 2.2, 3.9, 12.8, and 22.2 months, respectively; for mB-GPA scores, OS was 2.0, 7.6, 16.2, and 22.2 months, respectively; and for uB-GPA scores, OS was 2.2, 4.8, 15.8, and 37.7 months, respectively. In our series, 10.6% (n= 21) of patients did not receive radiotherapy and local brain therapy, which may explain the shorter survival compared to the original cohorts.[17-19] However, the 9.9-month OS is consistent with real-world data and SEER-based population study results published in 2019.[33,34]

All three prognostic indices seem sufficient to distinguish patients with very poor prognosis (OS < 3 months). However, uB-GPA is considered a better test with a higher C-index (0.689) and better discriminates patients who survive more than 3 years compared to B-GPA and mB-GPA. However, it is debated whether these tests should distinguish a larger group of patients with an approximately 2-year prognosis or a smaller number of patients with an excellent 3-year prognosis.[35]

The updated B-GPA index includes age, performance status, histological subtype, BMC, and ECM status.[19] In our study, the prognostic value of uB-GPA components (excluding tumor subtype) was confirmed. Additionally, ECD progression and spread were identified as two important independent risk factors. Although patients with good performance status are reported to have longer survival, performance status is a subjective assessment and may carry bias. Similarly, biological age often differs from chronological age. Nowadays, BM volume and lesion location appear to be more important than BMC alone.[36,37] Tumor subtype and ECD status are the main prognostic factors for OS. ECD status is typically classified as the presence or absence of distant metastases excluding the brain.[9,11,19,38,39]

Many studies have shown that ECD progression has a significant impact on OS and has been included in various prognostic indices.[6,12,14,40] Ahn et al. (2000-2008, n= 171) and Zhuang et al. (2006-2017, n= 282) identified ECD control as an independent risk factor for OS (p= 0.0002, MVA [HR] > 2.16 and p< 0.001, MVA [HR] 2.16, respectively).[12,30] When Zhuang et al. included ECD progression as a variable in the mB-GPA test, the C-index increased from 0.65 to 0.69 (30). Bottosso et al. investigated the prognostic significance of ECD progression in the HER2+ group (2002-2021, n= 113). OS for patients with ECD progression (57.7%, n= 65) was 8.7 months, while it was 17.7 months for other patients. ECD status retained its independent prognostic value after adjustment for confirmed uB-GPA (MVA [HR] 0.63, p= 0.040).[41] In our study, 96 (48.2%) patients had ECD progression at the time of BM. OS for these patients was 4.1 months, significantly shorter compared to 20.4 months for patients with ECD control, and ECD progression retained its independent prognostic value (MVA [HR] 2.45, p< 0.0001). Including ECD progression as a variable in the uB-GPA test increased the C-index to 0.709. OS for patients with uB-GPA scores of 0-1.0, 1.5-2.0, 2.5-3.0, and 3.5-4.0 with ECD control was 1.5, 12.6, 19.6, and 38.8 months, respectively. This was longer than the corresponding period for uB-GPA scores, except for the 0-1.0 band. Although ECM status was included in the recently updated B-GPA test, the potential prognostic impact of ECD progression was not evaluated.[19]

Recently, Shi W et al. (2008-2018, n= 445) evaluated the independent prognostic effect of the total number of intracranial and extracranial lesions rather than ECM status. The total number of metastatic lesions (≤ 5) was found to be a significant predictor of OS (MVA [HR] 0.55, p< 0.001). In 113 (25.4%) patients with ≤ 5 metastatic lesions at the time of BM diagnosis, MS was 24.3 months,

compared to 12.2 months in the other group. In patients with ≤ 5 metastatic lesions and uB-GPA scores of 0-1.0, 1.5-2.0, 2.5-3.0, and 3.5-4.0, OS was found to be 9.8, 22.8, 28.8, and 71.0 months, respectively. This was longer than the corresponding period for uB-GPA scores.[42]

This study has several strengths and weaknesses. To our knowledge, this is the first validation of all three prognostic indices in the Turkish population. A relatively large cohort of breast cancer patients treated at a single center, with long-term follow-up and a high event rate, was included. Despite efforts to avoid bias, the retrospective nature of the study is its major limitation. Patients were selected from a wide time range, so the possibility that patients in the same subgroup received different treatments cannot be overlooked. All our patients were symptomatic, as cranial imaging was performed only for those with neurological symptoms, in accordance with guideline recommendations.[43] Therefore, no information is available on the course of asymptomatic BCBM patients. Additionally, since a small portion of the patient group with ECD progression fell within the 0-1.0 band, we were unable to analyze this subgroup.

Conclusion

In summary, ECD significantly improves OS prediction both as an independent prognostic factor and when combined with existing prognostic tools. The inclusion of this factor enhances the predictive power of uB-GPA, enabling more accurate prognosis determination in clinical practice. However, with the emergence of effective systemic therapies and changing drug scales, the importance of these prognostic tools, as demonstrated by retrospective studies, may diminish in the future. Additionally, these prognostic indices, often developed by a single center, need to undergo external validation in different patient groups and larger populations.

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