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Validation of the graded prognostic assessment and recursive partitioning analysis as prognostic tools using a modern cohort of patients with brain metastases

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Abstract

Background. Prognostic indices for patients with brain metastases (BM) are needed to individualize treatment and stratify clinical trials. Two frequently used tools to estimate survival in patients with BM are the recursive partitioning analysis (RPA) and the diagnosis-specific graded prognostic assessment (DS-GPA). Given recent advances in therapies and improved survival for patients with BM, this study aims to validate and analyze these 2 models in a modern cohort.

Methods. Patients diagnosed with BM were identified via our institution's Tumor Board meetings. Data were retrospectively collected from the date of diagnosis with BM. The concordance of the RPA and GPA was calculated using Harrell's *C* index. A Cox proportional hazards model with backwards elimination was used to generate a parsimonious model predictive of survival.

Results. Our study consisted of 206 patients diagnosed with BM between 2010 and 2019. The RPA had a prediction performance characterized by Harrell's *C* index of 0.588. The DS-GPA demonstrated a Harrell's *C* index of 0.630. A Cox proportional hazards model assessing the effect of age, presence of lung, or liver metastases, and Eastern Cooperative Oncology Group (ECOG) performance status score of 3/4 on survival yielded a Harrell's *C* index of 0.616. Revising the analysis with an uncategorized ECOG demonstrated a *C* index of 0.648.

Conclusions. We found that the performance of the RPA remains unchanged from previous validation studies a decade earlier. The DS-GPA outperformed the RPA in predicting overall survival in our modern cohort. Analyzing variables shared by the RPA and DS-GPA produced a model that performed analogously to the DS-GPA.

Keywords

brain metastases | GPA | predictive models | prognostic factors | RPA

Prognostication tools are imperative in patients with brain metastases (BM) for 2 reasons: to guide clinical decision-making to optimally select a treatment regimen that coincides with patients' goals of care and to provide a tool to stratify clinical trials. The 2 main prognostic tools used to predict survival in patients with BM include the recursive partitioning analysis (RPA) and the graded prognostic assessment (GPA). Both predictive models integrate similar prognostic factors that correlate with the systemic burden of the disease as well as frailty.

The RPA was developed in 1997 using a database of 1200 patients with BM. Three classes were produced that represent different prognoses based on age, Karnofsky Performance Scale (KPS), primary tumor control, and extracranial metastases; Class I coincides with the best prognosis and Class 3 represents the worst prognosis.[1] The median overall survival

(mOS) of the entire group was 4.4 months.[1] However, survival varied when patients were stratified into different classes; Class 1 was described as 7.1 months and the survival of Class III was 2.3 months.[1]

The GPA is a similar prognostic tool that was developed in 2008. The original GPA found and used 4 factors (age, KPS, extracranial metastases, and number of BM) to predict survival.[2] These factors are weighted to develop a prognostic score between 0.0 (worst prognosis) and 4.0 (best prognosis). The GPA has been updated several times to include the primary diagnosis and diagnosis-specific (DS) molecular markers and other prognostic factors such as PD-L1.[3–7] The DS-GPA shows that both estimates of mOS and the significant prognostic factors for each primary diagnosis vary widely. Survival has improved but varies widely by GPA for patients with non-small-cell lung, breast, melanoma, GI, and renal cancer with brain metastases from 2 to 52 months, 3 to 36 months, 5 to 34 months, 3 to 17 months, and 4 to 35 months, respectively.[3,4] There is a free user-friendly online application to estimate survival available at brainmetgpa.com.

The RPA and GPA remain in use, however, the mOS of patients with BM has almost doubled since the inception of the RPA.[8,9] There have been significant advances in the treatments for BM since these 2 predictive models were published. Although many systemic therapies historically have been ineffective in treating BM, recent advances in targeted treatments and immunotherapies have shown efficacy in improving survival in individuals with primary lung cancer, breast cancer, and melanoma.[9–14] Additionally, the development of stereotactic radiosurgery (SRS) alone or as an adjunct to whole brain radiotherapy (WBRT) to treat multiple BM has proven to be an effective and less invasive way to treat BM and prevent recurrence with fewer adverse effects compared to WBRT.[15–17] Furthermore, laser interstitial thermal therapy (LITT) has emerged more recently with promising results in patients with BM.[18–20] The RPA and GPA were developed prior to the emergence of many new therapies. Therefore, we hypothesized that their prognostic validity would likely be impacted by these more recent treatment breakthroughs.

Given the importance that predicting survival in the BM patient population has on guiding treatment strategies, we sought to assess the validity of the GPA and RPA in predicting survival in a modern cohort of patients with BM. We then determined whether modifications to the current predictive tools would offer improved prediction performance in describing survival.

Methods

Ethics Statement

This study was conducted and approved by the appropriate institutional review board Pro00090408 under the waiver of consent.

Study Population

We included patients ≥18 years old, diagnosed with BM between May 2010 and September 2019. Patients were identified via their presentation at our institution's Brain and Spinal Metastasis Tumor Board, a multidisciplinary neurooncological team. Two total subjects were excluded from the analysis: 1 subject presented with lung cancer of unknown histology and an additional subject had a suspected malignant lesion that was determined to be benign. This study was conducted under our institution's IRB-reviewed protocol #00090408.

Variables

Clinical factors and oncological history were obtained from the date of original diagnosis with BM. Variables obtained include the date of BM diagnosis, primary tumor type, molecular markers of the primary tumor (ALK and EGFR for non-small cell lung cancer (NSCLC) adenocarcinoma, ER/PR/Her2 for breast cancer, and BRAF for melanoma), PD-L1 status, number of brain metastases, control of primary disease, presence of leptomeningeal disease, hemoglobin, white blood cell count, previous systemic therapy, presence of lung or liver metastases, presence of spine metastases, performance status (KPS or Eastern Cooperative Oncology Group (ECOG)), and date of death or last contact date. Patients with lung primary disease were considered to have lung metastases if nodules distinct from the primary lesion were found on follow-up imaging. ECOG was utilized as the standardized metric for performance status. Patients with performance status recorded in only KPS were converted to ECOG using conversion tables presented by Oken and colleagues.[21] Demographic variables collected included age, sex, ethnicity, and race.

Statistical Analysis

Expected survival per the RPA and GPA were calculated as described by the original RPA score and Sperduto's GPA, including the updated 2022 scoring system for lung cancers.[1,3,4] Within the context of a proportional hazards model, the relationship between RPA (or GPA) expected survival and actual survival from the time of brain metastasis diagnosis was examined. The goodness of fit was examined through the calculation of Harrell's *C* index.[22–24] A *C* index below 0.5 is an indication of a very poor model. A value of 0.5 means that the model is no better at predicting an outcome than random chance. Values over 0.7 indicate a good model. Values over 0.8 indicate a strong model.[22–24]

The Cox proportional hazards model was initially used to assess the joint effect of age (uncategorized), presence of lung or liver metastases, and ECOG performance status 3 or 4 on survival time from diagnosis with BM. The relationship between these predictions and actual survival from the time of BM diagnosis was examined within a Cox model with the calculation of Harrell's *C* index.

Results

Demographics

This sample consisted of 206 patients who presented to our institution's Brain and Spine Metastasis Tumor Board from

Table 1. Patient Demographics

Characteristic	Number (%)
Sex	
Female	126 (61)
Male	80 (39)
Race	
Caucasian/White	152 (74)
Black/African American	41 (20)
Asian	4 (2)
Other[a]	9 (4)
Primary diagnosis	
NSCLC—Adenocarcinoma	77 (37)
Breast	49 (24)
NSCLC—Non-Adenocarcinoma	24 (12)
Melanoma	23 (11)
GI[b]	16 (8)
Renal	10 (5)
SCLC	7 (3)
ECOG performance status	
0	55 (27)
1	98 (48)
2	32 (16)
3	19 (9)
4	2 (1)
Presence of lung or liver metastases	
Yes	116 (56)
No	90 (44)

[a]Includes patients identifying as other (2), 2 or more races (1), and declined to report (6).
[b]GI malignancies were comprised of colorectal (5), esophageal (4), pancreatic (2), rectal (2), hepatocellular carcinoma (2), and gastric (1) cancer primary.

February 8, 2018 to October 1, 2019. These patients were diagnosed with BM between May 6, 2010 and September 24, 2019.

With respect to demographics, patient-reported gender was 126 (61%) females and 80 (39%) males (Table 1). Regarding race, 152 (74%) of patients identified as Caucasian/White, 41 (20%) as Black or African American, 4 (2%) as Asian, and 9 (4%) as Other (Table 1). Primary diagnosis favored lung malignancy with 101 (49%) having NSCLC, which was further categorized as NSCLC-adenocarcinoma 77 (37%) and NSLC-non-adenocarcinoma 24 (12%), and 7 (3%) having small-cell lung cancer (SCLC) (Table 1). The remainder of primary diagnoses consisted of 49 (24%) breast, 23 (11%) melanoma, 16 (8%) gastrointestinal (GI), and 10 (5%) renal (Table 1).

Oncological factors included ECOG and the presence of lung or liver metastasis; at the time of diagnosis with BM. Regarding ECOG, 55 (27%) patients had a score of 0, 98 (48%) patients scored 1, 32 (16%) had an ECOG of 2, 19 (9%) patients had a score of 3, and 2 (1%) patients had an ECOG score of 4 (Table 1). 116 (56%) patients had lung or liver metastases and 90 (44%) of patients did not have lung or liver metastases (Table 1). Six total patients developed concurrent leptomeningeal disease.

Survival Analysis

152 of the 206 patients with BM died during the study period with mOS of 28.1 months (95% CI: 22.2, 34.0) from BM diagnosis. When stratified by primary diagnosis, patients with renal cell carcinoma had an mOS of 48.7 months (95% CI: 1.8, 107.8), breast cancer had an mOS of 39.2 months (95% CI: 20.7, 44.5), NSCLC: Adenocarcinoma had an mOS of 32.8 months (95% CI: 26.4, 52.8), NSCLC: Non-Adenocarcinoma had an mOS of 18.6 months (95% CI: 7.2, 34.0), SCLC had an mOS of 9.0 months (95% CI: 1.2, 23.4), melanoma had an mOS of 18.2 months (95% CI 11.1, 65.2), and GI malignancy had an mOS of 11.9 months (95% CI: 5.4, 16.3, Figure 1A).

Grouped by performance status, patients with an ECOG of 0 had an mOS of 50.9 months (95% CI: 34.0, 95.8). Patients with an ECOG of 1 had an mOS of 28.1 months (95% CI: 21.8, 38.0). Patients with an ECOG of 2 had an mOS of 12.9 months (95% CI: 5.9, 30.3). An ECOG of 3 was associated with an mOS of 11.9 months (95% CI: 3.1, 22.2) and patients with an ECOG of 4 had an mOS of 7.4 months (95% CI: 1.7, 13.2, Figure 1B).

Patients younger than 65 years had mOS of 32.1 (95% CI: 23.2, 42.6). mOS of patients older than or equal to 65 years old was 25.5 (95% CI: 16.3, 31.5, Figure 1C).

Concordance Between Models Predicted Survival and Actual Survival

Harrell's *C* index was computed to assess the goodness of fit of predicted survival by the models compared to actual survival. 88% of patients lived longer than expected per the RPA (Table 2a). The *C* index associated with the survival model that includes expected survival per the RPA as a predictor in the model is 0.588.

The *C* index associated with the survival model that includes expected survival per the GPA as a predictor is 0.630. 77% of the patients lived longer than expected per the GPA prognostic tool (Table 2b). There are 3 total patients who remain alive and have been followed for a period of time that is less than the expected survival.

A Cox proportional hazards model was used to assess the effect of age, presence of lung or liver metastases, and performance status on survival time from diagnosis (Table 3). Harrell's *C* index using this model was 0.616. Performing a similar analysis with an uncategorized ECOG demonstrated a *C* index of 0.648 (Table 4).

Discussion

Validation of prognostication tools is imperative to ensure ongoing predictive accuracy given constant innovation in therapies that enhance survival. Our work sought

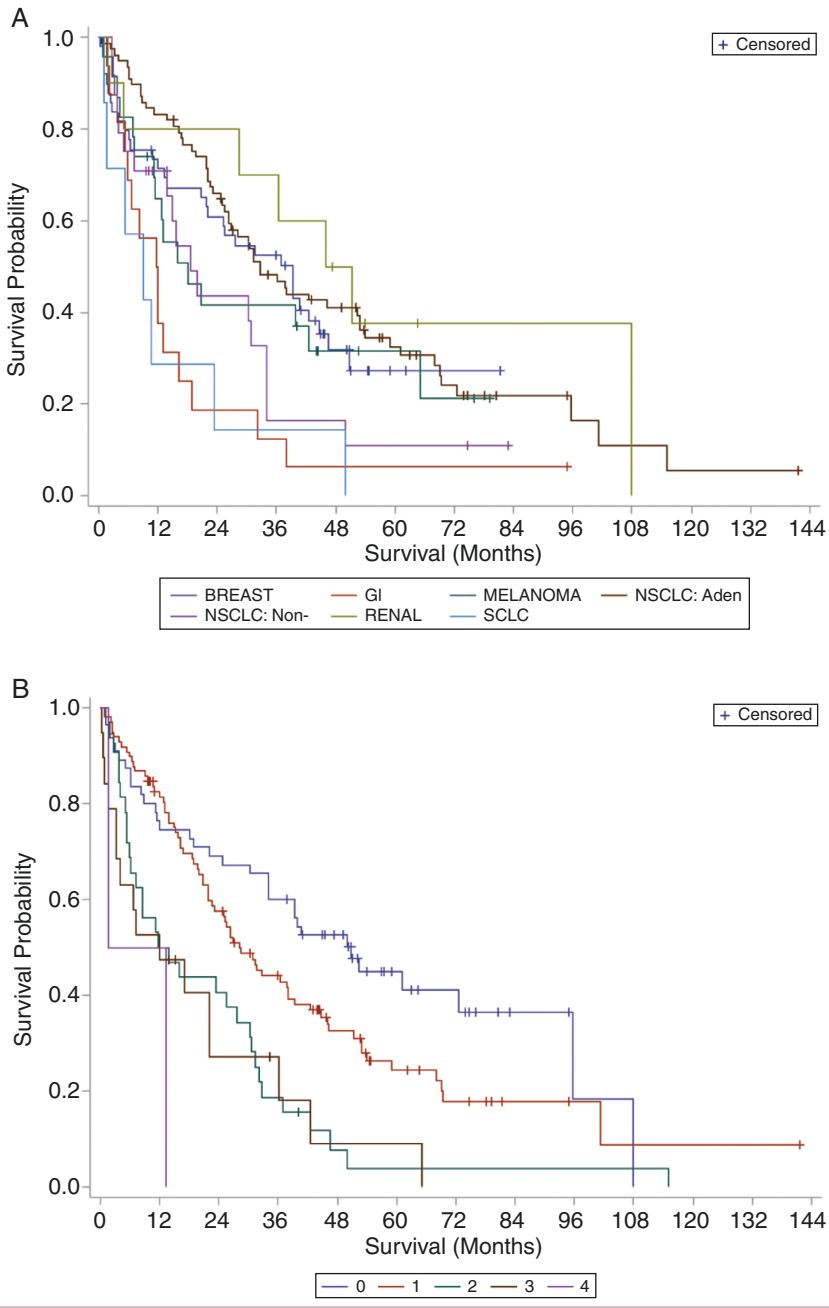
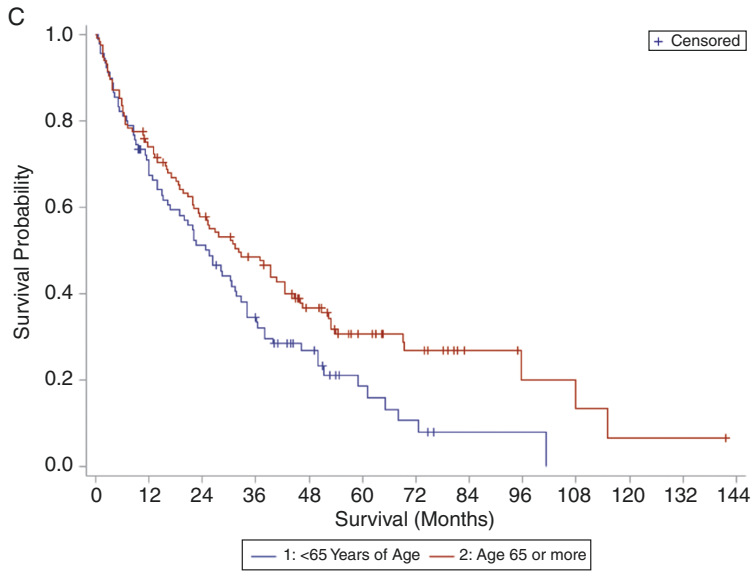


Figure 1. Survival is stratified by diagnosis, ECOG, and age. Kaplan–Meier survival curves stratified by: (A) primary diagnosis*, (B) ECOG performance status**, and (C) age***. * Median survival (95% CI): Breast 37.0 (20.7, 44.5), GI 11.9 (5.4, 16.3), NSCLC: Adenocarcinoma 18.6 (7.2, 34.0), NSCLC: Non-Adenocarcinoma 32.7 (26.2, 52.8), Melanoma 18.2 (11.1, 62.2), Renal 48.7 (1.8, 107.8). ** Median survival (95% CI): ECOG 0: 50.9 (34.0, 95.8), ECOG 1: 28.5 (22.6, 39.3), ECOG 2: 12.9 (6.2, 30.3), ECOG 3: 11.9 (3.1, 22.1), ECOG 4: 7.4 (1.7, 13.2) *** Median survival (95% CI): Age <65: 32.7 (23.2, 44.5), Age ≥65: 25.5 (16.8, 32.8)

to assess the prediction performance of 2 validated prognostic tools for BM using a modern cohort of patients. Survival was not described well by the RPA and diagnosis-specific (DS) GPA, with Harrell's *C* indices nearing 0.5 suggesting a noninformative prediction model.[25] Relative to the RPA, the DS-GPA demonstrated improved concordance in predicting survival. While the DS-GPA performed better than the RPA, the 3 variables contained within the RPA demonstrated analogous to slightly improved survival prediction performance using a Cox proportional hazards model.

Historically, the RPA and original GPA have been shown to perform relatively equivalently in predicting survival. Our data demonstrate enhanced prediction performance of the DS-GPA.[26]

The RPA and GPA share many prognostic factors, namely age, performance status, and extracranial metastases. These factors have remained consistent predictors



*mOS (95% CI): Breast 39.2 (20.7, 44.5), GI 11.9 (5.4, 16.3), NSCLC: Non-Adenocarcinoma 18.6 (7.2, 34.0), NSCLC: Adenocarcinoma 32.8 (26.4, 52.8), Melanoma 18.2 (11.1, 65.2), Renal 48.7 (1.8, 107.8), SCLC 9.0 (1.2, 23.4).

**mOS (95% CI): ECOG 0: 50.9 (34.0, 95.8), ECOG 1: 28.1 (21.8, 38.0), ECOG 2: 12.9 (5.9, 30.3), ECOG 3: 11.9 (3.1, 22.1), ECOG 4: 7.4 (1.7, 13.2)
***mOS (95% CI): Age <65: 32.1(23.2, 42.6), Age ≥65: 25.5 (16.3, 31.5)

Figure 1. Continued

Table 2. Relationship Between Predicted Survival Per the (A) RPA[a] and (B) GPA[b] and Observed Survival

	Dead—Did not Live Longer than Expected		Dead—Lived Longer than Expected			Censored—Lived Longer than Expected	
(A)	***N***	**%**	***N***		**%**	***N***	**%**
All patients	24	11.65	128	62.14		54	26.2136
Breast	8	16.33	24	48.98		17	34.6939
GI	3	18.75	12	75.00		1	6.2500
Melanoma	3	13.04	13	56.52		7	30.4348
NSCLC—Adenocarcinoma	4	5.19	53	68.83		20	25.9740
NSCLC—Non-Adenocarcinoma	3	12.50	15	62.50		6	25.0000
Renal	1	10.00	6	60.00		3	30.0000
SCLC	2	28.57	5	71.43		0	0
(B)	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**
All patients	48	23.30	104	50.49	51	24.7573	3	1.46
Breast	16	32.65	16	32.65	16	32.6531	1	2.04
GI	8	50.00	7	43.75	1	6.2500	0	0.00
Melanoma	8	34.78	8	34.78	6	26.0870	1	4.35
NSCLC—Adenocarcinoma	10	12.99	47	61.04	20	25.9740	0	0.00
NSCLC—Non-Adenocarcinoma	4	16.67	14	58.33	5	20.8333	1	4.17
Renal	2	20.00	5	50.00	3	30.0000	0	0.00
SCLC	7	5.92	6.73	0.03	0.16	5.84	9.84	18.36

[a]Harrell's *C* index = 0.588.
[b]Harrell's *C* index = 0.630.

Table 3. Parsimonious Cox Model to Assess the Effect of Age, Lung/Liver, and ECOG on Survival Time from BM Diagnosis.[a]

Analysis of Maximum Likelihood Estimates								
Parameter	DF	Parameter estimate	Standard error	Chi-Square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits	
Age	1	0.02520	0.00819	9.4667	0.0021	1.026	1.009	1.042
Presence of lung or live metastases	1	0.57605	0.17185	11.2357	0.0008	1.779	1.270	2.491
ECOG PS 3 or 4	1	1.05241	0.26051	16.3193	<0.0001	2.865	1.719	4.773

[a]Harrell's *C* index = 0.616.

Table 4. Parsimonious Cox Model to Assess the Effect of Age, Lung/Liver, and Uncategorized ECOG on Survival Time From BM Diagnosis[a]

Parameter		DF	Parameter estimate	Standard error	Chi-square	Pr > ChiSq	Hazard ratio	95% Hazard ratio confidence limits	
Age		1	0.02214	0.00826	7.1793	0.0074	1.022	1.006	1.039
Presence of lung or live metastases		1	0.52846	0.17962	8.6562	0.0033	1.696	1.193	2.412
ECOG	**1 vs 0**	1	0.44699	0.21457	4.3396	0.0372	1.564	1.027	2.381
ECOG	**2 vs 0**	1	0.87151	0.26023	11.2161	0.0008	2.391	1.435	3.981
ECOG	**3 vs 0**	1	1.39649	0.31861	19.2115	< 0.0001	4.041	2.164	7.545
ECOG	**4 vs 0**	1	1.92810	0.73942	6.7995	0.0091	6.876	1.614	29.293

[a]Harrell's *C* index = 0.648.

of survival over time, likely reflecting a combination of systemic disease burden and physiologic reserve. Older patients are more likely to have other comorbid conditions, which may impact the treatments they are eligible to receive.[27,28] Though few studies have examined the relationship between performance status and disease burden, poor KPS scores have been associated with pathophysiological changes, such as cerebrospinal fluid (CSF) leukocytosis in individuals with leptomeningeal metastases.[29] Peripheral leukocytosis may indirectly reflect granulocyte-colony stimulating factor (G-CSF), which may play a role in tumor progression.[30–32] Finally, the presence of extracranial metastases or multiple BM signifies advanced disease and limits effective therapeutic intervention.[33]

Given the similarities between the DS-GPA and RPA, we assessed whether the shared variables comprising these systems would offer a more robust prediction performance if weighted differently. Using a Cox proportional hazards model, we found that age, lung or liver metastases, and ECOG of 3 or 4 performed similarly to the original RPA in predicting survival. Implementing the same model but with an uncategorized ECOG performance score increased the *C* index to slightly higher than that of the DS-GPA. As there were only 2 patients with an ECOG of 4, the increase in prediction performance is likely attributable to the subgroups of patients with performance scores between 0 and 2. Therefore, careful investigation of the performance status of seemingly healthier patients may offer valuable information regarding survival. In summary, these results suggest that age, visceral metastases, and performance status offer insights into survival that are equivalent to those provided by stratifying survival by primary diagnosis and molecular markers.

The need to continuously update and validate BM prognostic indices is emphasized by the patient cohorts underlying each predictive model. The RPA reflects an analysis of patients from 1979 to 1993 whereas the original GPA describes a cohort of patients from 1985 to 2007.[1,2] The GPA was revised with diagnosis-specific data using a sample of patients diagnosed with BM from 2006 and 2017.[26] The 2022 Lung GPA uses a dataset of patients diagnosed with BM from 2015 to 2020, incorporating SCLC into the analysis as well as the effect of PD-L1 status.[3] A breadth of oncological, chemotherapeutic, and surgical interventions have been pioneered within the window of 1979–2017 that have been shown to dramatically improve survival in cancer patients, particularly those with BM.[4,34–39] These advances include the discovery of HER2 in 1984, a determination that surgical resection and WBRT improved outcomes for single brain metastasis in 1990, FDA approval of trastuzumab in 1998, work in 2004 demonstrating WBRT and SRS improves survival for patients with single brain metastasis, and FDA authorization of immunotherapy for the treatment of lung cancer in 2014.[40–44] These transformations in the management of cancer may underlie the increase in mOS of patients with BM from 4.4 months in 1997 to 7.16 months in 2008.[1,2] More recent work from 2021 assessing the efficacy of LITT for the management of BM has shown improved survival. An mOS of 17.15 months was achieved in patients who had recurrent BM in the field of SRS after treatment with LITT.[18,19] LITT in conjunction with SRS for BM recurrence improved median time to lesion progression to 29.8 months, compared to 7.5 months and 3.7 months from LITT alone and SRS alone, respectively.[20] The mOS in our cohort was 30.3 months which may reflect improved outcomes for BM due to modern

therapies or a variety of other factors such as referral bias or selection bias.

There are several limitations to our work. The cohort used in this analysis consists of patients who were presented at our institution's Brain and Spine Metastasis Tumor Board. The retrospective nature of our analyses may result in selection bias favoring patients with BM who survived longer durations. The select group of patients presented at the Tumor Board may not be representative of the entire brain metastasis population, particularly those with severe diseases that may not require discussion at the Tumor Board. Additionally, female patients comprised a majority of the cohort and primary disease was heavily skewed towards lung and breast primary.

Future studies are warranted for continued validation of prognostic tools in the BM population. Additional work exploring sociodemographic factors associated with survival in the BM population would offer interesting information that has been minimally addressed in prognostic tools. Further studies investigating diagnosis-specific subgroup survival as influenced by line of therapy and prior treatments might offer more value to a diagnosis-specific prediction model. Predictive models accounting for small cell lung cancer would offer valuable information for this patient population.

Conclusion

The evolving landscape of oncological therapies for BM necessitates validation and updates to existing prognostication tools. The RPA and GPA are widely validated tools for predicting survival in the BM population and remain in use today. Our analyses revealed similar prediction performance of the RPA from previous reports. The more recently updated DS-GPA performed better than the RPA in our cohort. A model created using factors shared by the RPA and DS-GPA, namely age, performance status, and the presence of visceral metastasis, demonstrated similar prediction performance to the DS-GPA. These results suggest that the DS-GPA may be superior to the RPA in predicting survival, however, revisions to the RPA may increase its accuracy to be comparable to that of the DS-GPA. Future studies will be valuable to continue demonstrating the accuracy of these prognostic tools to identify which factors should remain salient to clinicians when managing patients with BM.

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Conflict of interest statement

The authors have no disclosures relevant to the current work, nor any true/perceived conflicts of interest. Disclosures unrelated to the current work include: P.E.F.: consultant for Monteris Medical; C.R.G.: received grants from the Robert Wood Johnson Harlod Amos Medical Faculty Development Program, the Federal Food and Drug Administration, and the NIH 1R01DE031053-01A1. Consultant for Stryker and Medtronic. Deputy Editor for Spine. Pending patents unrelated to the current work; T.J.Z.: pending patents unrelated to the current work. J.S.: pending patents unrelated to the current work. All other authors have no disclosures unrelated to the current work.

Authorship statement

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by J.S., T.D., and J.E.H. The first draft of the manuscript was written by J.S. and S.Y. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

Data will be made available upon reasonable request.

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