Survival in Patients With Brain Metastases: Summary Report on the Updated Diagnosis-Specific Graded Prognostic Assessment and Definition of the Eligibility Quotient

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abstract

PURPOSE Conventional wisdom has rendered patients with brain metastases ineligible for clinical trials for fear that poor survival could mask the benefit of otherwise promising treatments. Our group previously published the diagnosis-specific Graded Prognostic Assessment (GPA). Updates with larger contemporary cohorts using molecular markers and newly identified prognostic factors have been published. The purposes of this work are to present all the updated indices in a single report to guide treatment choice, stratify research, and define an eligibility quotient to expand eligibility.

METHODS A multi-institutional database of 6,984 patients with newly diagnosed brain metastases underwent multivariable analyses of prognostic factors and treatments associated with survival for each primary site. Significant factors were used to define the updated GPA. GPAs of 4.0 and 0.0 correlate with the best and worst prognoses, respectively.

RESULTS Significant prognostic factors varied by diagnosis and new prognostic factors were identified. Those factors were incorporated into the updated GPA with robust separation ($P < .01$) between subgroups. 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 7-47 months, 3-36 months, 5-34 months, 3-17 months, and 4-35 months, respectively.

CONCLUSION Median survival varies widely and our ability to estimate survival for patients with brain metastases has improved. The updated GPA (available free at brainmetgpa.com) provides an accurate tool with which to estimate survival, individualize treatment, and stratify clinical trials. Instead of excluding patients with brain metastases, enrollment should be encouraged and those trials should be stratified by the GPA to ensure those trials make appropriate comparisons. Furthermore, we recommend the expansion of eligibility to allow for the enrollment of patients with previously treated brain metastases who have a 50% or greater probability of an additional year of survival (eligibility quotient > 0.50).

INTRODUCTION

Exclusion of patients with brain metastases from clinical trials not only raises issues of equity and discrimination, but, given the high incidence of brain metastases, hinders accrual to and limits the generalizability of those trials. These patients are often excluded as a result of three main concerns. First, investigators fear that the historically poor outcomes associated with brain metastases could mask the benefit of the treatment under investigation.[1-3] Second, because neurologic symptoms could occur, new investigational agents risk having these symptoms associated with the agent itself, a risk that many pharmaceutical companies avoid. Third, many pharmaceutical agents have poor blood-brain and brain-tumor penetrability, decreasing the likelihood of meaningful intracranial efficacy. An estimated 300,000

patients are diagnosed each year with brain metastases in the United States, and the incidence is growing because of advances that have resulted in patients living longer and hence at increased risk for brain metastases.[4] For example, a recent review of patterns of failure in 1,549 patients with stage 1 to stage 3 non–small-cell lung cancer (NSCLC), 466 (30%) developed recurrence, most commonly brain metastases (37%).[5]

The brain metastases challenge is a complex problem because of the marked heterogeneity of this patient population: Brain metastases may arise from a wide variety of primary tumors, patients may have already received several different treatments for their primary cancer, and resistance to multiple lines of therapy is common. This heterogeneity has plagued the interpretation of clinical trials involving this patient population because of the difficulty in accurately stratifying those studies to ensure similar groups were being compared. The complexity is further compounded by the many possible combinations of available treatments for brain metastases (surgery, stereotactic radiosurgery [SRS], whole-brain radiation therapy [WBRT], chemotherapy, molecularly targeted therapeutics, and immunotherapies).

These concerns led to efforts to understand and quantitatively model prognosis. Our group has published a series of articles developing and refining a diagnosis-specific prognostic index, the Graded Prognostic Assessment (GPA), for patients with brain metastases. The GPA was first published in 2008[6] on the basis of 1,960 patients from five randomized Radiation Therapy Oncology Group (RTOG) trials (RTOG 7916, RTOG 8528, RTOG 8905, RTOG 9104, and RTOG 9508). Analysis showed that four prognostic factors—age, Karnofsky performance status (KPS), extracranial metastases, and number of brain metastases—were significant for survival. Those prognostic factors were weighted in proportion to their significance and scaled such that patients with the best or worst prognosis would have a GPA of 4.0 or 0.0, respectively. In 2010, we refined the GPA when we discovered that survival varies by primary diagnosis and diagnosis-specific prognostic factors based on a retrospective analysis of 3,940 patients.[7] The Breast GPA was then further refined using tumor molecular subtype.[8] In 2012, we published an executive summary report that was based on 3,940 patients with newly diagnosed brain metastases diagnosed between 1993 and 2010.[9]

Since the publication of the 2012 executive report, GPA indices have been updated for each diagnosis with larger contemporary cohorts using molecular markers and newly identified clinical prognostic factors.[10-18] Of most importance, the treatment paradigms for most patients with brain metastases have evolved over the last decade. Our purpose is to report all the updated diagnosis-specific GPAs in a single report that can be used to individualize treatment, stratify clinical trials, and define the eligibility quotient (EQ) to expand clinical trial eligibility.

METHODS

Patient Population

A multi-institutional (18 institutions in three countries), institutional review board–approved, retrospective database of 6,984 patients with newly diagnosed brain metastases diagnosed between 2006 and 2017 was created using Research Electronic Data Capture software. Patients with recurrent brain metastases and/or leptomeningeal carcinomatosis were excluded.

Statistics

Survival was measured from the date of the first treatment of brain metastases to the date of death or last follow up. We used the Kaplan-Meier method to calculate all survival estimates. Treatment comparisons were made using a multiple Cox proportional hazards regression model that included categorical variables for initial treatment combination and GPA class. Analysis was performed using R software (version 3.4).

Derivation of GPA Indices

The common approach for deriving GPA indices was to use multiple Cox proportional hazards regression to identify an initial set of prognostic factors. These factors were then weighted, using half or full point increments, according to the magnitude of effect on survival—that is, hazard ratio. The final index was chosen by balancing criteria that included separation of prognostic classes, the percentage of patients in each class, and simplicity. Such metrics as the concordance index, R^2, and log-rank test statistics were used to evaluate model performance. In general, marginally significant factors were retained only if they afforded nontrivial improvements to the final index. Factors initially considered included those that were already significant in previous GPA versions and additional factors that varied by primary cancer type that were hypothesized to be associated with survival—for example, molecular markers, sex, and body mass index. Details of the variables collected and specific methods used for each cohort may be found in the publication of each diagnosis-specific GPA.[6-18]

Role of Funding Source

The funding sources for this study had no role in the collection, analysis, or interpretation of the data; the writing of the report; or the decision to submit it for publication.

RESULTS

Patient Characteristics

Table 1 lists patient characteristics for the overall data set. The proportions of patients who were asymptomatic (KPS = 100) for breast, lung adenocarcinoma, lung non-adenocarcinoma, renal, melanoma, and GI cancers were 7%, 6%, 9%, 9%, 13%, and 7%, respectively. Most patients had extracranial metastases. In lung adenocarcinoma, 15% and 6% of patients were *EGFR* and *ALK*

TABLE 1. Patient Characteristics and Median Survival by Diagnosis

Characteristic	Breast Cancer No. (%)	Breast Cancer MS (IQR)	NSCLC Adenocarcinoma No. (%)	NSCLC Adenocarcinoma MS (IQR)	NSCLC Nonadenocarcinoma No. (%)	NSCLC Nonadenocarcinoma MS (IQR)	Renal Cell Carcinoma No. (%)	Renal Cell Carcinoma MS (IQR)	Melanoma No. (%)	Melanoma MS (IQR)	GI Cancers No. (%)	GI Cancers MS (IQR)
Overall	2,473	16 (7-34)	1,521	15 (6-32)	665	9 (4-19)	710	12 (4-30)	823	10 (4-26)	792	8 (3-18)
KPS at BM diagnosis												
100	184 (7)	23 (12-42)	94 (6)	25 (12-49)	57 (9)	14 (7-33)	62 (9)	28 (10-102)	110 (13)	17 (8-42)	55 (7)	16 (7-26)
90	720 (29)	20 (9-43)	513 (34)	18 (7-39)	199 (30)	10 (4-25)	179 (25)	20 (9-49)	343 (42)	12 (6-32)	187 (24)	12 (6-21)
80	652 (26)	15 (6-32)	419 (28)	16 (6-30)	181 (27)	10 (5-19)	194 (27)	13 (5-26)	192 (23)	8 (3-20)	207 (26)	7 (3-18)
70	371 (15)	11 (4-22)	332 (22)	10 (4-22)	150 (23)	6 (3-13)	144 (20)	6 (3-14)	102 (12)	6 (3-11)	154 (19)	6 (3-13)
≤ 60	195 (8)	5 (2-17)	123 (8)	6 (2-21)	63 (9)	4 (1-9)	106 (15)	5 (2-13)	76 (9)	7 (2-12)	113 (14)	3 (1-8)
Unknown	351 (14)	22 (11-46)	40 (2.6)	20 (13-32)	15 (2.3)	14 (7-17)	25 (3.5)	20 (7-47)	0		76 (10)	10 (4-19)
Age at BM diagnosis, years												
< 50	872 (35)	19 (8-43)	199 (13)	20 (8-43)	61 (9)	11 (6-21)	91 (13)	15 (4-38)	192 (23)	15 (6-40)	134 (17)	11 (4-20)
50-59	791 (32)	18 (7-34)	414 (2)	17 (7-34)	208 (31)	12 (4-21)	207 (29)	13 (5-35)	221 (27)	9 (4-25)	205 (26)	10 (4-19)
60-69	565 (23)	13 (5-29)	540 (36)	16 (6-35)	238 (36)	9 (4-21)	247 (35)	11 (4-32)	238 (29)	10 (4-24)	275 (35)	7 (3-18)
70-79	200 (8)	11 (5-27)	299 (20)	10 (4-23)	133 (20)	6 (3-12)	133 (19)	11 (4-25)	142 (17)	7 (4-16)	128 (16)	5 (2-14)
≥ 80	43 (1.7)	9 (3-13)	69 (4.5)	8 (4-20)	25 (3.8)	6 (2-9)	32 (4.5)	9 (3-13)	30 (3.6)	8 (2-21)	50 (6)	6 (2-12)
ECM at BM diagnosis												
Present	1,997 (81)	15 (6-32)	858 (56)	11 (4-23)	347 (52)	7 (3-16)	604 (85)	11 (4-26)	687 (83)	9 (4-20)	622 (79)	7 (3-15)
Absent	454 (18)	23 (11-51)	623 (41)	22 (10-46)	301 (45)	12 (5-22)	83 (12)	36 (11-61)	136 (17)	20 (8-66)	150 (19)	14 (6-26)
Unknown	22 (0.9)	21 (14-34)	40 (2.6)	10 (4-20)	17 (2.6)	8 (4-10)	23 (3.2)	8 (4-19)	0		20 (2.3)	9 (3-18)
No. of BM at initial diagnosis												
1	869 (35)	20 (9-45)	650 (43)	16 (6-38)	328 (49)	9 (4-18)	380 (54)	16 (5-40)	328 (40)	12 (6-36)	379 (48)	10 (4-22)
2	387 (16)	18 (7-36)	301 (20)	15 (6-34)	130 (20)	9 (4-21)	137 (19)	12 (5-24)	151 (18)	10 (5-30)	152 (19)	7 (3-18)
3	230 (9)	13 (5-27)	168 (11)	15 (5-30)	84 (13)	10 (4-21)	77 (11)	9 (4-26)	96 (12)	7 (4-30)	85 (11)	8 (3-14)
4	165 (7)	13 (7-30)	87 (6)	17 (5-29)	38 (6)	9 (5-25)	34 (4.8)	8 (2-14)	56 (7)	8 (4-15)	35 (4.4)	3 (1-10)
5-9	301 (12)	14 (5-31)	145 (10)	15 (6-25)	48 (7)	8 (2-16)	61 (9)	6 (2-17)	103 (13)	9 (4-19)	84 (11)	4 (2-13)
≥ 10	486 (20)	12 (4-28)	135 (9)	11 (3-24)	22 (3.2)	10 (1-15)	21 (3.0)	6 (2-16)	89 (11)	6 (2-12)	40 (5.0)	2 (1-7)
Unknown	35 (1.4)	23 (16-46)	35 (2.3)	15 (5-29)	15 (2.3)	9 (4-17)	0		0		17 (2.1)	12 (8-18)
Subtype												
ER/PR/HER2+	527 (21)	27 (13- 55)										
ER/PR/HER2−	595 (24)	9 (4-19)										
ER/PR−/HER2+	421 (17)	25 (11-47)										
ER/PR+/HER2−	772 (31)	14 (5-30)										
Unknown	158 (6)	14 (5-29)										
EGFR												
Positive			235 (15)	23 (11-45)								
Negative			697 (46)	15 (6-34)								
Not tested			589 (39)	12 (5-24)								
ALK												
Positive			86 (6)	44 (20-NR)								
Negative			654 (43)	17 (6-35)								
Not tested			781 (51)	12 (5-25)								
Hemoglobin at BM diagnosis												
(5.5, 11.2)							135 (19)	5 (2-11)				
(11.2, 12.6)							131 (18)	11 (4-25)				

(continued on following page)

TABLE 1. Patient Characteristics and Median Survival by Diagnosis (continued)

Characteristic	Breast Cancer		NSCLC Adenocarcinoma		NSCLC Nonadenocarcinoma		Renal Cell Carcinoma		Melanoma		GI Cancers	
	No. (%)	MS (IQR)	No. (%)	MS (IQR)	No. (%)	MS (IQR)	No. (%)	MS (IQR)	No. (%)	MS (IQR)	No. (%)	MS (IQR)
(12.6, 14.4)							143 (20)	16 (7-42)				
≥ 14.4							134 (19)	18 (7-47)				
Unknown							167 (24)	15 (6-40)				
BRAF												
Positive									297 (36)	13 (6-33)		
Negative									287 (35)	9 (5-24)		
Not tested									239 (29)	8 (3-17)		

Abbreviations: BM, brain metastases; ECM, extracranial metastases; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; KPS, Karnofsky performance status; MS, median survival; NR, not reached; NSCLC, non–small-cell lung cancer; PR, progesterone receptor.

positive, respectively. In melanoma, 36% were *BRAF* positive.

Table 2 lists median survival by diagnosis and GPA. Compared with our prior summary report,[9] overall median survival for patients with brain metastases from all diagnoses has improved in more recent analyses, from 7-12 months—15 months for lung adenocarcinoma—for NSCLC; from 14-16 months for breast cancer; from 7-10 months for melanoma; from 5-8 months for GI cancers; and from 10-12 months for renal cell carcinoma. Table 2 also shows that the range of median survival by GPA is wide, 7-46 months for NSCLC, 3-36 months for breast cancer, 5-34 months for melanoma, 3-17 months for GI cancers, and from 4-35 months for renal cell carcinoma. Figure 1 shows the Kapan-Meier curves for survival by diagnosis and the updated GPA, demonstrating excellent separation between groups ($P < .01$) and the median survival for each GPA group (0-1 month, 1.5-2.0 months, 2.5-3.0 months, and 3.5-4.0 months). Table 3 provides a user-friendly worksheet with which to calculate the GPA for an individual patient. A free online application is also available at brainmetgpa.com.

Effect of Treatment

The purpose of prognostic indices is to predict outcomes before treatment, thereby helping the clinician select treatment by balancing risks versus benefit with knowledge of anticipated survival, which is in contrast to predictive tools that predict outcomes after treatment. Therefore, the data presented in Table 4, a multivariable analysis of the risk of death and median survival by treatment and diagnosis, are not intended to show that one treatment is better than another. These data are retrospective with inherent selection bias and therefore cannot be used to compare treatments. Nonetheless, Table 4 does show patterns of care and can be compared with those patterns in the prior era. For instance, the percentage of patients receiving WBRT as part of initial therapy in the prior era compared with our current data decreased from 75%-

37% in NSCLC adenocarcinoma and from 67%-47% in breast cancer.[7,9] This is consistent with randomized trials demonstrating that SRS alone is equally effective in terms of survival and associated with fewer neurocognitive deficits, albeit with a much greater likelihood of intracranial relapse than SRS plus WBRT.[19,20]

Summary of Changes to the Indices

The larger contemporary database allowed us to identify new and more robust prognostic factors, including mutations, which have been incorporated into the updated GPA indices. All of the previously identified factors were confirmed.

NSCLC. Changes in the updated Lung GPA (n = 2,186)[10,11] compared with the original Lung GPA (NSCLC, n = 1,833)[7,9] include, for lung adenocarcinoma, the addition of two new factors (*EGFR* and *ALK* gene alterations). There were no changes in the Lung GPA for nonadenocarcinoma.

Breast cancer. Changes in the updated Breast GPA[12] compared with the original Breast GPA[8,9] include the addition of two new factors, extracranial metastases and the number of brain metastases, which were found to be significant in the new breast data (n = 2,473).

Melanoma. Changes in the updated Melanoma-mol GPA (n = 823)[13,14] compared with the original Melanoma GPA (n = 481)[7,9] include the addition of three new factors (*BRAF* status, age, and extracranial metastases).

Renal cell carcinoma. Changes in the updated Renal GPA (n = 710)[15,16] compared with the original Renal GPA (n = 286)[7,9] include the addition of two new factors (extracranial metastases and hemoglobin).

GI carcinomas. Changes in the updated GI GPA (n = 792)[17,18] compared with the original GI GPA (n = 209)[7,9] include the addition of three factors (age, number of brain metastases, and extracranial metastases).

TABLE 2. MS by Diagnosis and Diagnosis-Specific GPA

Diagnosis	Overall		GPA 0.0-1.0		GPA 1.5-2.0		GPA 2.5-3.0		GPA 3.5-4.0	
	No.	MS (IQR), Months	No. (%)	MS (IQR), Months	No. (%)	MS (IQR), Months	No. (%)	MS (IQR), Months	No. (%)	MS (IQR), Months
Breast cancer	2,473	16 (7-34)	376 (19)	6 (2-12)	769 (39)	13 (6-27)	654 (33)	24 (11-47)	173 (9)	36 (18-78)
NSCLC adenocarcinoma	1,521	15 (6-32)	289 (20)	7 (2-15)	616 (43)	13 (5-24)	453 (32)	25 (11-53)	64 (5)	46 (25-NA)
NSCLC nonadenocarcinoma	665	9 (4-19)	153 (25)	5 (2-10)	304 (49)	10 (4-21)	164 (26)	13 (7-29)	0 (0)	NA
Renal cell carcinoma	710	12 (4-30)	168 (25)	4 (2-8)	179 (27)	12 (4-25)	204 (31)	17 (8-36)	117 (18)	35 (13-61)
Melanoma	823	10 (4-26)	136 (17)	5 (2-11)	386 (47)	8 (4-18)	256 (31)	16 (8-49)	45 (5)	34 (15-NA)
GI cancers	792	8 (3-18)	217 (31)	3 (2-8)	184 (27)	7 (3-17)	211 (30)	11 (4-21)	80 (12)	17 (9-30)
Overall	6,984	13 (5-29)	1339 (22)	5 (2-11)	2438 (39)	11 (4-23)	1942 (31)	20 (9-43)	479 (8)	33 (15-66)

Abbreviations: GPA, Graded Prognostic Assessment; IQR, interquartile range; MS, median survival; NA, not available; NSCLC, non–small-cell lung cancer.

DISCUSSION

Guidelines

Three current evidence-based guidelines assert the primary role of local therapies—resection, SRS, and WBRT with or without hippocampal avoidance—in the management of patients with brain metastases.[21-23] These treatments are supported by multiple randomized clinical trials that have changed the standard of care.[19,20,24-27]

Regarding systemic therapy in patients with breast cancer with brain metastases, an ASCO Clinical Practice Guideline Update recommended that patients with human epidermal growth factor receptor 2 (HER2)–positive breast cancer and brain metastases receive appropriate local therapies—resection, SRS, or WBRT—and HER2-targeted therapies, making it clear that local therapies remain the mainstay of initial management for brain metastases.[23]

Each of these guidelines emphasizes the importance of understanding prognosis to optimally individualize treatment. This report refines our understanding of prognosis and summarizes newly discovered prognostic factors, confirming that prognosis varies by both histopathologic and molecular diagnosis. The updated diagnosis-specific GPA offers a more accurate method with which to estimate survival. Such information will guide clinical decision making, patient choice, and end-of-life care, and will be useful in the stratification of future clinical trials to ensure that those trials are comparing comparable patients.

Improvement in survival. Comparison of survival between our prior summary report[9] and this report shows improvement for all included diagnoses. The cause is undoubtedly multifactorial. In patients with lung adenocarcinoma with *EGFR* or *ALK* gene alterations and brain metastases, survival in the best prognostic group (GPA, 3.5-4.0) is now a remarkable 47 months. This is consistent with randomized data showing the efficacy of third-generation tyrosine kinase inhibitors (osimertinib) in these patients.[28]

In patients with breast cancer with brain metastases, not only has overall survival improved, but for patients in the best prognostic group (Breast GPA, 3.5-4.0), median survival is now 36 months. Furthermore, in the HER2 subtype, our data show that median survival has improved from 18 months to 25 months.[8,9] For HER2-positive patients with CNS progression after initial local therapy, a number of HER2-directed regimens offer the potential for durable responses in some patients.[29-31] Whereas our data set has limitations, in light of the frequent exclusions of patients with brain metastases in prospective clinical trials and the inclusion only of de novo stage IV patients in the population-based SEER registry,[32] we believe that our observations represent perhaps the most persuasive evidence to date of the impact of advances in local and systemic therapy on the outcomes of patients with HER2-positive breast cancer and brain metastases in a real-world scenario.

In patients with melanoma with brain metastases, randomized phase II data show that dual immune checkpoint inhibition—ipilimumab and nivolumab—has some efficacy in the small percentage of patients without symptoms.[33,34] Our data show that only 13% of patients with melanoma brain metastases do not have symptoms (KPS = 100; Table 1), again affirming the primary role of local therapies—SRS with or without craniotomy—for the vast majority of patients.

The search for drug therapies for these patients has been thwarted by poor blood-brain and brain-tumor penetrability. Another complicating factor is receptor status or gene alteration discordance between the primary tumor and brain metastasis. In breast cancer, for instance, the frequency of receptor gain for estrogen receptor, progesterone receptor, and HER2 was 18%, 14%, and 13%, respectively. The frequency of receptor loss for estrogen receptor, progesterone receptor, and HER2 was 26%, 49%, and 7%, respectively.[35] If actionable receptors are lost, survival
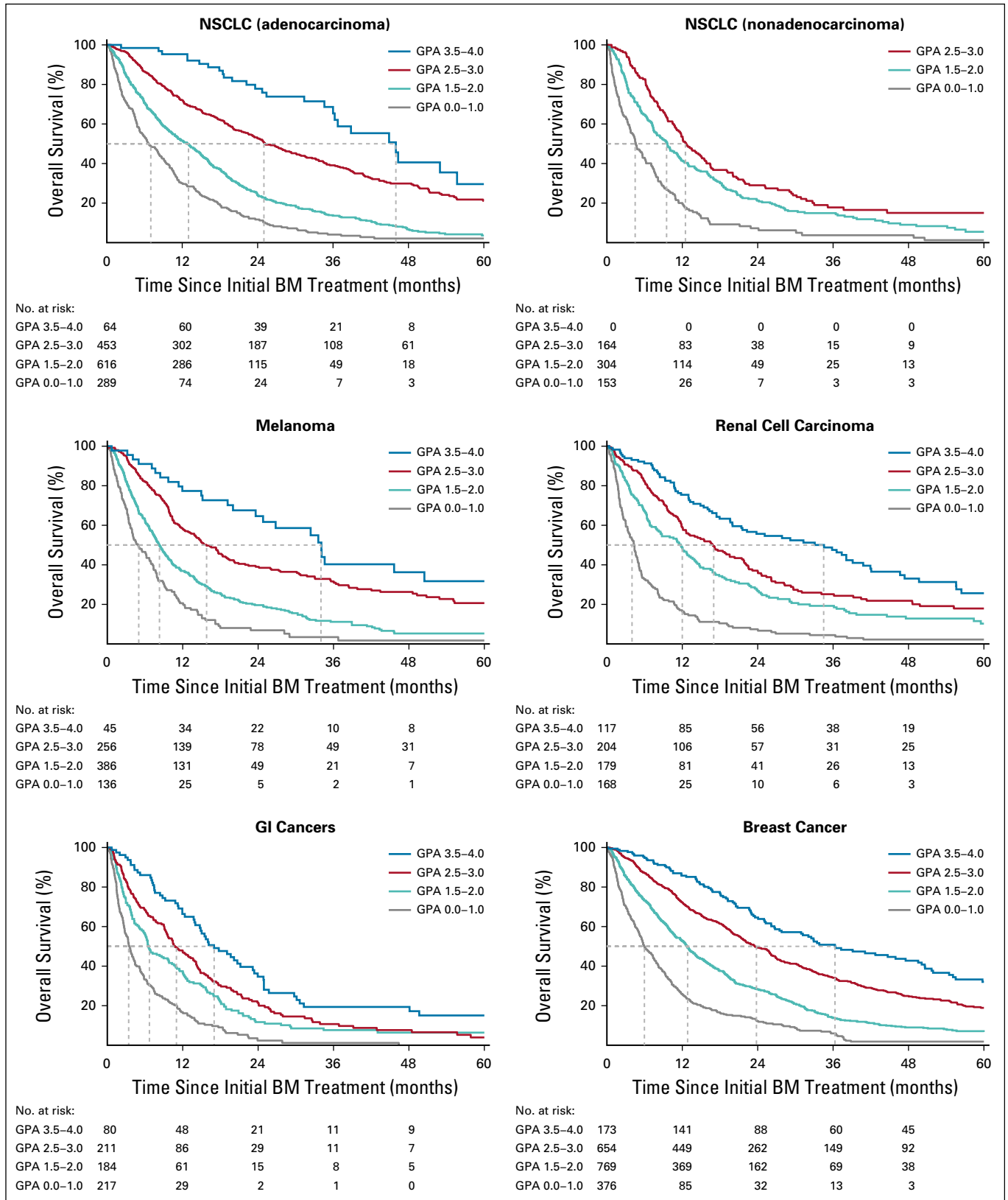
FIG 1. Kaplan-Meier curves for survival by diagnosis and the updated diagnosis-specific Graded Prognostic Assessment (GPA). BM, brain metastases; NSCLC, non–small-cell lung cancer;

TABLE 3. Worksheet for Calculation of the Diagnosis-Specific GPA

Prognostic Factor by Cancer Type	GPA					Patient Score
	0	0.5	1.0	1.5	2.0	
Breast cancer						
KPS	≤ 60	70-80	90-100	NA	NA	
Age, years	≥ 60	< 60	NA	NA	NA	
No. of BM	≥ 2	1	NA	NA	NA	
ECM	Present	Absent	NA	NA	NA	
Subtype	Basal	Luminal A	NA	Her2 or Luminal B	NA	
					Sum =	MS (months) by GPA: 0-1 = 6; 1.5-2.0 = 13; 2.5-3.0 = 24; 3.5-4.0 = 36
NSCLC adenocarcinoma						
KPS	≤ 70	80	90-100	NA	NA	
Age, years	≥ 70	< 70	NA	NA	NA	
No. of BM	≥ 5	1-4	NA	NA	NA	
ECM	Present	NA	Absent	NA	NA	
EGFR and ALK	Both negative or unknown	NA	EGFR or ALK positive	NA	NA	
					Sum =	MS (months) by GPA: 0-1 = 7; 1.5-2.0 = 13; 2.5-3.0 = 25; 3.5-4.0 = 46
NSCLC nonadenocarcinoma						
KPS	≤ 70	80	90-100	NA	NA	
Age, years	≥ 70	< 70	NA	NA	NA	
No. of BM	≥ 5	1-4	NA	NA	NA	
ECM	Present	NA	Absent	NA	NA	
					Sum =	MS (months) by GPA: 0-1 = 5; 1.5-2.0 = 10; 2.5-3.0 = 13; 3.5-4.0 = NA
Renal cell carcinoma						
KPS	≤ 70	NA	80	NA	90-100	
No. of BM	≥ 5	1-4	NA	NA	NA	
ECM	Present	Absent	NA	NA	NA	
Hgb	< 11.1	11.1-12.5 or unknown	> 12.5	NA	NA	
					Sum =	MS (months) by GPA: 0-1 = 4; 1.5-2.0 = 12; 2.5-3.0 = 17; 3.5-4.0 = 35
Melanoma						
KPS	≤ 70	80	90-100	NA	NA	
Age, years	≥ 70	< 70	NA	NA	NA	
No. of BM	≥ 5	2-4	1	NA	NA	
ECM	Present	NA	Absent	NA	NA	
BRAF	Negative or unknown	Positive	NA	NA	NA	
					Sum =	MS (months) by GPA: 0-1 = 5; 1.5-2.0 = 8; 2.5-3.0 = 16; 3.5-4.0 = 34

TABLE 3. Worksheet for Calculation of the Diagnosis-Specific GPA (continued)

Prognostic Factor by Cancer Type	GPA					Patient Score
	0	0.5	1.0	1.5	2.0	
GI cancers						
KPS	≤ 70	NA	80	NA	90-100	
Age, years	≥ 60	< 60	NA	NA	NA	
No. of BM	≥ 4	2-3	1			
ECM	Present	Absent	NA	NA	NA	

Sum =   MS (months) by GPA: 0-1 = 3; 1.5-2.0 = 7; 2.5-3.0 = 11; 3.5-4.0 = 17

NOTE. Breast cancer subtypes: basal = triple negative (ER/PR/HER2−); Luminal A (ER/PR+, HER2−); Luminal B (triple positive, ER/PR/HER2+); HER2 (HER2+, ER/PR−).

Abbreviations: BM, brain metastases; ECM, extracranial metastases; GPA, Graded Prognostic Assessment; Hgb, hemoglobin; KPS, Karnofsky performance status; MS, median survival; NA, not available; NSCLC, non–small-cell lung cancer.

would decline. If actionable receptors are gained, targeted therapies may be of benefit. These discordance data lead to the practical clinical recommendation that whenever a patient undergoes resection of a brain metastasis, relevant receptors or gene alteration studies should be performed. This represents another layer of heterogeneity, and because the GPA incorporates molecular factors, the prognostic impact of receptor discordance is also reflected in these indices.

Has the GPA been used in clinical trials? Multiple reports have used the GPA. Among these are four secondary analyses of prospective randomized clinical trials that have defined the current standard of care ([RTOG 9508,[36] JROSG 99-1,[37] EORTC 22952-26001,[38] and NCCTG-N0574[39]) and two trials that incorporated the GPA into the initial analysis (RTOG 0320[40] and RTOG 1119[41]). Two trials in development stratify by the GPA: NRG-BN-2026 (SRS plus ipilimumab/nivolumab in melanoma brain metastases) and Canadian Cancer Trials Group (SRS for five to 15 brain metastases).[42]

How can adoption of the GPA enhance enrollment of patients with brain metastases in clinical trials? These data have several specific implications for clinical management and future research. Patients with brain metastases have been routinely considered to be ineligible for clinical trials because of the obsolete conventional wisdom that their outcomes are uniformly grim and inclusion would mask the benefit of otherwise promising treatments. This obstructs progress and discriminates against patients with brain metastases. Including patients with brain metastases in clinical trials would be consistent with the recommendations of the ASCO-Friends of Cancer Research eligibility working group[1] and the Response Assessment in Neuro-Oncology Brain Metastasis Working Group,[43] and in line with US Food and Drug Administration guidance.[44]

The GPA can be used to enhance the enrollment of patients with brain metastases in clinical trials, including not only trials investigating treatments for brain metastases, but also a much broader spectrum of trials investigating treatments

unrelated to brain metastases. We recommend the expansion of eligibility to include any otherwise eligible patient with brain metastases if their median survival, as defined by the GPA, is 1 year or greater. If the primary focus of a proposed trial is unrelated to brain metastases, the trial would ideally be—but need not be—stratified by the GPA as long as the eligibility is expanded as suggested and a subgroup analysis is performed by GPA class. Failure to stratify by the GPA, however, could render the trial uninterpretable, resulting in an enormous waste of time and resources. Improved survival for subsets of patients with brain metastases should be sufficient for enrolling them in clinical trials of systemic agents.

Definition of the EQ. Clinical trialists should ask how exactly the GPA can be used to allow enrollment of patients with previously treated brain metastases in clinical trials. The GPA is based on patients with newly diagnosed brain metastases. Nonetheless, the GPA scale can also be used for patients with previously treated brain metastases. Kaplan-Meier GPA curves can be used to estimate remaining survival time, which is conditional on surviving some amount of time after the initial treatment of brain metastases. For example, consider a GPA of 2.0 in a patient with breast cancer who is eligible for a clinical trial 6 months after the treatment of brain metastases. Should she be eligible for that trial? Yes, because her expected survival of 6 months after the treatment of brain metastases would be approximately 75% (Fig 1). The survival percentage 1 year later—18 months after the treatment of brain metastases—is approximately 40%. Using the conditional probability equation, EQ = (survival percentage at time t + 12 months)/survival percentage at time t, where EQ = eligibility quotient and t = survival percentage at the time (months) after the treatment of brain metastases, we can calculate EQ = 40/75 = 0.54. We recommend that any patient with an expected survival of 50% or greater for at least 1 additional year (EQ ≥ 0.50) be eligible for clinical trials. This is

TABLE 4. Multivariable Analysis of Risk of Death and Median Survival by Treatment and Diagnosis

Cancer Type	All	WBRT	SRS	WBRT + SRS	S + SRS	S + WBRT	S + WBRT + SRS	None
Breast cancer								
No. (%)	2,473	903 (37)	840 (34)	105 (4)	261 (11)	136 (5)	18 (1)	210 (8)
Mean GPA	2.0	1.8	2.1	2.1	2.2	2.3	2.5	2.4
Median survival	16	13	16	15	19	25	24	23
Risk of death (HR)		1.00	0.90	1.03	0.71	0.73	0.87	0.68
95% CI			0.80 to 1.01	0.81 to 1.30	0.60 to 0.85	0.59 to 0.90	0.51 to 1.51	0.57 to 0.83
P			.07	.83	< .01	< .01	.63	< .01
Lung cancer (NSCLC), adenocarcinoma								
No. (%)	1,521	342 (22)	767 (50)	139 (9)	114 (7)	76 (5)	13 (1)	70 (5)
Mean GPA	2.0	1.7	2.1	1.7	2.3	2.0	2.3	2.3
Median survival	15	13	14	10	31	20	19	24
Risk of death (HR)		1.00	1.07	1.15	0.70	0.64	0.83	0.72
95% CI			0.91 to 1.25	0.90 to 1.46	0.53 to 0.93	0.48 to 0.87	0.43 to 1.61	0.53 to 0.97
P			.43	.28	.01	< .01	.59	.03
Lung cancer (NSCLC), nonadenocarcinoma								
No. (%)	665	98 (15)	342 (51)	103 (15)	51 (8)	40 (6)	4 (1)	27 (4)
Mean GPA	1.8	1.6	1.8	1.7	2.0	2.0	1.3	2.2
Median survival	9	11	7	8	11	16	12	13
Risk of death (HR)		1.00	1.54	1.57	1.04	0.77	0.56	0.90
95% CI			1.19 to 2.00	1.11 to 2.21	0.69 to 1.54	0.50 to 1.19	0.17 to 1.82	0.55 to 1.48
P			< .01	.01	.86	.25	.33	.68
Renal cell carcinoma								
No. (%)	710	90 (13)	409 (58)	41 (6)	70 (10)	23 (3)	4 (1)	73 (10)
Mean GPA	2.1	1.7	2.2	2.1	2.1	1.9	2.6	2.2
Median survival	12	5	11	11	24	16	11	22
Risk of death (HR)		1.00	0.71	0.70	0.35	0.43	1.86	0.40
95% CI			0.53 to 0.95	0.46 to 1.07	0.23 to 0.54	0.25 to 0.74	0.64 to 5.35	0.27 to 0.58
P			.02	.10	< .01	< .01	.25	< .01
Melanoma								
No. (%)	823	91 (11)	464 (56)	73 (9)	95 (12)	34 (4)	12 (1)	54 (7)
Mean GPA	2.0	1.5	2.1	1.8	2.1	1.8	1.9	2.1
Median survival	10	6	10	9	13	11	11	17
Risk of death (HR)		1.00	0.69	0.67	0.52	0.59	0.69	0.52
95% CI			0.52 to 0.90	0.47 to 0.96	0.36 to 0.74	0.37 to 0.93	0.35 to 1.34	0.34 to 0.78
P			.01	.03	< .01	.02	.28	< .01
GI cancers								
No. (%)	792	166 (21)	309 (39)	31 (4)	121 (15)	67 (8)	5 (1)	93 (12)
Mean GPA	1.9	1.3	2.0	1.8	2.2	2.1	1.6	2.4
Median survival	8	3	6	12	11	14	4	14
Risk of death (HR)		1.00	0.95	0.73	0.51	0.55	0.69	0.55
95% CI			0.75 to 1.20	0.47 to 1.13	0.38 to 0.69	0.40 to 0.77	0.23 to 2.04	0.40 to 0.75
P			.66	.16	< .01	< .01	.50	< .01

NOTE. HR, 95% CI, and P value (each treatment v WBRT alone within each cohort) from Cox proportional hazards model adjusted for GPA and stratified by institution. Median survival is unadjusted in months.

Abbreviations: GPA, Graded Prognostic Assessment score; HR, hazard ratio; NSCLC, non–small-cell lung cancer; S, surgery; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

a conservative cutoff, given that the end points of most phase I and II trials are tumor response or progression-free survival, which are usually determined before 1 year.

Guiding supportive care. The GPA also identifies patients with the worst prognosis. Patients with a GPA of 0.0-1.0 have a poor prognosis and conservative management and/ or hospice should be considered. Randomized data suggest that supportive care is not inferior to WBRT in patients with a poor prognosis.[45] Patients with brain metastases from GI cancers had the highest percentage (31%) of extremely poor prognosis (GPA = 0.0-1.0).

Limitations

Limitations of this study include the retrospective design and inherent selection biases; because of selection bias, these data cannot be used to conclude the superiority of one treatment over another. In addition, patients who were not treated for their brain metastases may not be included in this database and hence these data may slightly overestimate survival for the overall population with brain metastases.

In conclusion, survival for patients with brain metastases has improved, but varies widely by histopathologic and molecular diagnosis and by diagnosis-specific prognostic factors. New prognostic factors, including molecular markers, have been identified and incorporated into the updated GPA indices. For each diagnosis, robust separation between GPA subgroups/score was discerned, confirming marked heterogeneity. The updated GPA, which was based on large contemporary cohorts, provides an accurate method with which to estimate survival and stratify clinical trials for patients with brain metastases. By including these patients in clinical trials, we expand eligibility, democratize research, enhance accrual, and speed progress. Furthermore, results of those trials will be more generalizable and thus better reflect the real world. The GPA is also useful for clinicians as they individualize treatment or guide supportive care on the basis of prognosis, regardless of whether the patient is in a clinical trial.

Lastly, instead of excluding patients with brain metastases from clinical trials, enrollment should be encouraged, and those trials should be stratified by the GPA to ensure that those trials make appropriate comparisons, and eligibility should be expanded by application of the EQ.

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DISCLAIMER

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Minnesota. The design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication was solely the responsibility of the authors and does not necessarily represent the official views of the funders/sponsors.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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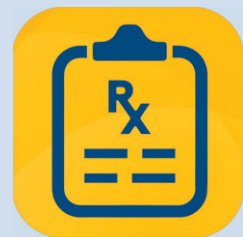
AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Survival in Patients With Brain Metastases: Summary Report on the Updated Diagnosis-Specific Graded Prognostic Assessment and Definition of the Eligibility Quotient

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Patents, Royalties, Other Intellectual Property: WARF patent 14/934,27, topical vasoconstrictor preparations and methods for protecting cells during cancer chemotherapy and radiotherapy
Uncompensated Relationships: Xcision Medical Systems, ViewRay

No other potential conflicts of interest were reported.