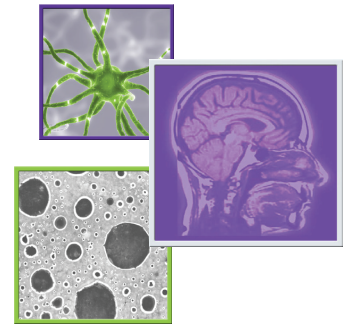
RESEARCH ARTICLE

CNS Oncology

Does Graded Prognostic Assessment outperform Recursive Partitioning Analysis in patients with moderate prognosis brain metastases?



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Practice points

- Optimal treatment for moderate prognosis patients (Recursive Partitioning Analysis [RPA] II or Graded Prognostic Assessment [GPA] 1.5–2.5) can be unclear.
- Treatment options for brain metastases include surgery, stereotactic radiosurgery, whole brain radiotherapy (WBRT), supportive measures or combinations of these modalities.
- Better prognosis patients are often prescribed longer schedules of whole brain radiation.
- On multivariable analysis among RPA II patients, receiving >10 WBRT fractions or undergoing surgery/stereotactic radiosurgery were significantly associated with increased survival.
- Among patients with GPA 1.5–2.5, better Karnofsky Performance Status or undergoing surgery/stereotactic radiosurgery were significantly associated with increased survival.
- The RPA II and GPA 1.5–2.5 have similar predicted median survivals (4.2 and 3.8 months), and in our patient group those scored by the RPA and assigned a longer radiation schedule had a survival advantage, while patients scored by the GPA did not.
- This could indicate the GPA is more clinically useful, leaving less room for subjective assessment in choosing treatment.
- There are many recently published articles concerning prognostic indices for brain metastases which are succinctly summarized in Tables 5 and 6 of this publication.

Aim: To compare the clinical utility of the Recursive Partitioning Analysis (RPA) and Graded Prognostic Assessment (GPA) in predicting outcomes for moderate prognosis patients with brain metastases. **Methods & materials:** We reviewed 101 whole brain radiotherapy cases. RPA and GPA were calculated. Overall survival was compared. **Results:** Sixty-eight patients had moderate prognosis. RPA patient characteristics for increased death hazard were ≤10 WBRT fractions or no surgery/radiosurgery. GPA patients had increased death risk with no surgery/radiosurgery or lower Karnofsky Performance Status. **Conclusion:** The indices have similar predicted survival. Patients scored by RPA with longer radiation schedules had longer survival; patients scored by GPA did not. This indicates GPA is more clinically useful, leaving less room for subjective treatment choices.

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KEYWORDS
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Over 170,000 cases of brain metastases are diagnosed in the USA each year, and the length of survival for these patients is often limited [1]. The Radiation Therapy Oncology Group Recursive Partitioning Analysis (RPA) and Graded Prognostic Assessment (GPA) are prognostic indices validated to predict survival and guide treatment for these patients [2–5]. These indices were formulated by comparing survival to patient characteristics compiled from brain metastasis treatment protocols across three decades.

The RPA has three classes of patients enumerated as 'I', 'II' and 'III,' with class I having the longest predicted survival and class III the shortest. The RPA classes are based upon age, Karnofsky performance status (KPS), control of the primary tumor and evidence of extracranial metastases **(Table 1)** [2]. The GPA has four classes with a score that may be considered analogous to a student's grade point average in school. The classes are arranged from best to worst prognosis as follows: 3.5 to 4.0, 3.0, 1.5–2.5 and 0.0–1.0. The GPA employs criteria that are slightly different than those used in the RPA, estimating survival by age, performance status, number of brain metastases and extracranial metastases **(Table 2)** [4].

Treatment options for brain metastases include surgery, stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), supportive measures or combinations of these modalities. The median survival (MS) of the worst prognosis patients is estimated by the RPA and GPA to be 2.3 and 2.6 months respectively [2,4]. In these patients, treatments are usually less aggressive and typically include WBRT and/or steroids. The best fractionation scheme is not well established, but there are many who favor shorter courses or supportive care only [6–8].

More aggressive treatment may produce better outcomes in good prognosis patients. There are data showing a survival advantage for patients with a single brain metastasis who receive surgery or SRS in addition to WBRT [9,10]. A recently reported meta-analysis of randomized trials of SRS ± WBRT in RPA I or II patients with one to four brain metastases revealed that, in patients ≤50 years old, survival was significantly better with SRS alone [11]. This is currently not the standard of care [12,13], but may affect future guidelines.

With 'moderate prognosis' patients (RPA II or GPA 1.5–2.5), treatment options become more variable. For these patients, the MS is 4.2 months for RPA II and 3.8 months for GPA 1.5–2.5 patients. Selecting the best treatment for patients in these categories is challenging, and there have been changes suggested to both the GPA and RPA to add more granularity. Specifically, Sperduto *et al.* have created the 'Diagnosis Specific-GPA' (DS-GPA) where the GPA score is adjusted based on the primary disease histology [5]. Similarly, Yamamoto *et al.* have published recommendations to subdivide the RPA II into three subgroups that represent the range of MS lengths within this group [14].

In our clinic, moderate prognosis patients who are expected to have more favorable outcomes based on their initial presentation will frequently receive more aggressive treatment for their brain metastases such as protracted WBRT regimens (generally 35–37.5 Gy in 14–15 fractions) with or without surgery or SRS. We were interested in evaluating the median survival in the patients who had moderate prognosis (RPA II or GPA 1.5–2.5). The objective of this study was to evaluate whether either the GPA or the RPA provided more useful guidance to clinicians. Here we retrospectively analyze 101 consecutive patients with brain metastases that had undergone WBRT, measured their survival in a nonprotocol setting and compared actual survival to that predicted by the RPA and GPA indices.

Materials & methods

Following study approval by our institutional review board, the charts of all consecutive brain metastasis patients treated with WBRT

Table 1. Recursive partitioning analysis.

Class	Patient characteristics	MS (months)
I	KPS ≥ 70, age < 65, no extracranial mets, controlled primary	7.1
II	All others, that is KPS ≥70 and at least one of the following: age ≥ 65 or extracranial mets or uncontrolled primary	4.2
III	KPS < 70	2.3

KPS: Karnofsky performance status; Mets: Metastases, MS: Median survival; RPA: Recursive Partitioning Analysis.

Table 2. Graded prognostic assessment.

Patient characteristics	GPA score		
	0	0.5	1.0
Age	≥60	50–59	<50
KPS	<70	70–80	90–100
CNS mets (n)	>3	2–3	1
Extra-cranial mets	Present	–	Absent
GPA grade (sum of GPA scores)	**MS (months)**		
3.5–4	11.0		
3	6.9		
1.5–2.5	3.8		
0–1	2.6		

GPA: Graded Prognostic Assessment; KPS: Karnofsky performance status; Mets: Metastases; MS: Median survival.

between August 2008 and September 2010 were reviewed. Reasons for exclusion from the study included primary brain tumors, <19 years old, diagnosis of multiple myeloma/leukemia/lymphoma, retreatment with WBRT and patients without evidence of parenchymal brain disease (i.e., leptomeningeal metastases, prophylactic treatment).

The inclusion criteria were met by 101 patients. A retrospective chart review collected the data for calculating each patient's RPA and GPA (Tables 1 & 2) as well as treatment details, including corticosteroid use and surgery and/or SRS. All patients had received MRIs. We based the number of brain metastases on the MRI report rather than review of MRI images. For 13 patients, KPS had to be retrospectively assigned from the radiation oncologist's consult note in cases where no KPS had been explicitly stated. For these, chart notes were examined for patient characteristics and exam findings to assign a KPS value. For five patients, KPS was converted from another performance status scale. To calculate survival time, the social security death

Table 3. Patient, disease and treatment characteristics.

	All patients (n = 101)		RPA II (n = 68)		GPA 1.5–2.5 (n = 61)	
	Mean	Range	Mean	Range	Mean	Range
Age	57.4	(31–82)	56.0	(38–82)	54.9	(31–82)
KPS	74.3	(50–100)	80.4	(70–100)	78.0	(50–100)
	n	%	n	%	n	%
Male	47	46.5	35	51.5	27	44.3
Female	54	53.5	33	48.5	34	55.7
Histology:						
NSCLC	47	46.5	26	38.2	26	42.6
Melanoma	12	11.9	12	17.6	8	13.1
Breast	12	11.9	7	10.3	6	9.8
SCLC	9	8.9	6	8.8	7	11.5
Other	21	20.8	17	25.0	14	23.0
Number CNS mets:						
– 1	19	18.8	11	16.2	14	23.0
– 2–3	36	35.6	24	35.3	25	41.0
– >3	46	45.5	33	48.5	22	36.0
Number of fractions:						
– ≤10	60	59.4	37	54.4	34	55.7
– >10	41	40.6	31	45.6	27	44.3
Surgery or SRS	32	31.7	22	32.4	23	37.7

There is overlap between RPA II and GPA 1.5–2.5 patients.
GPA: Graded Prognostic Assessment; KPS: Karnofsky performance status; Mets: Metastases; NSCLC: Non-small-cell lung cancer; RPA: Recursive Partitioning Analysis; SCLC: Small-cell lung cancer; SRS: Stereotactic radio surgery.

Table 4. Univariate survival.

	Hazard ratio (95% CI)	p-value
RPA II		
Age (increase of 10 years)	1.47 (1.10–1.97)	0.0095
KPS (decrease of 5 points)	1.20 (1.02–1.41)	0.0321
Sex (male vs female)	1.94 (1.11–3.40)	0.0204
Histology:		0.5432
– Breast vs NSCLC	0.57 (0.19–1.67)	
– Melanoma vs NSCLC	1.06 (0.47–2.33)	
– SCLC vs NSCLC	1.75 (0.69–4.41)	
Number CNS mets:		
– 2–3 vs 1	1.85 (0.74–4.67)	0.2035
– >3 vs 1	2.25 (0.92–5.52)	
Number of fractions (≤10 vs >10)	2.51 (1.40–4.47)	0.0019
Surgery or SRS (no vs yes)	4.74 (2.31–9.71)	<0.0001
GPA 1.5–2.5		
Age (increase of 10 years)	1.20 (0.88–1.63)	0.2553
KPS (decrease of 5 points)	1.21 (1.08–1.36)	0.0015
Sex (male vs female)	1.35 (0.75–2.41)	0.3184
Histology:		0.1454
– Breast vs NSCLC	0.41 (0.12–1.37)	
– Melanoma vs NSCLC	0.75 (0.28–2.01)	
– SCLC vs NSCLC	2.19 (0.91–5.29)	
Number CNS mets:		
– 2–3 vs 1	0.85 (0.41–1.73)	0.5985
– >3 vs 1	0.67 (0.31–1.46)	
Number of fractions (≤10 vs >10)	1.89 (1.04–3.43)	0.0373
Surgery or SRS (no vs yes)	2.83 (1.48–5.43)	0.0017

GPA: Graded Prognostic Assessment; KPS: Karnofsky performance status; Mets: Metastases; NSCLC: Non-small-cell lung cancer; RPA: Recursive Partitioning Analysis; SCLC: Small-cell lung cancer; SRS: Stereotactic radio surgery.

index was used for date of death or ongoing survival.

Statistical methods

Each patient was assigned an RPA and GPA score and was then grouped by those. Survival was calculated from the time of the WBRT consult date. MS was calculated using the Kaplan–Meier method. The associations of the categorical variables of RPA class and GPA grade with overall survival were examined with a log–rank test. Univariate Cox-proportional hazards models were done among patients with RPA II and also GPA 1.5–2.5 to investigate the association between sex, histology (NSCLC, melanoma, breast, SCLC, other), inclusion of surgery/SRS, number of CNS metastases (1, 2–3, >3), number of fractions (≤10 vs >10), age and KPS with overall survival. Multivariable Cox proportional hazards models were fit including all factors with univariate p-value <0.25. A backward selection approach was used to determine the final model.

Results

The mean (±SD) patient age was 57.4 (±10.6) years. Fifty-three percent were female (54 of 101). Forty-seven percent had NSCLC (47 of 101) and 12% each had melanoma and breast cancer (12 of 101 respectively). Patient and disease characteristics are shown in Table 3.

Of the 101 cases, the number that fit the RPA I, II and III classes were 8, 68 and 25 patients, respectively. The 68 RPA II patients in this study showed a median survival of 4.8 months (95% CI: 3.5–6.0 months). The predicted median survival of 4.2 months per the RTOG RPA falls within the 95% CI in our dataset.

All patients were also grouped according to the GPA index. This analysis showed that 2, 3, 61 and 35 patients resided in the 4 GPA classes; 3.5–4.0, 3.0, 1.5–2.5 and 0.0–1.0, respectively. For the 61 patients in the GPA 1.5–2.5, the median survival was 5.0 months (95% CI: 4.3–8.0). In this case, the predicted MS of 3.8

months per the GPA index is outside the 95% CI of the actual MS in our dataset.

Survival varied significantly according to prognostic class. The survival of patients in RPA I versus II versus III was significantly different (MS 7.1, 4.8 and 2.4 months, respectively, p = 0.0016). Survival significantly differed by GPA grade (MS not yet achieved, 5.0 and 2.4 months for GPA grades 3.0–4.0, 1.5–2.5 and 0.0–1.0, respectively, p < 0.0001).

A total of 84 patients were in either the RPA II or the GPA 1.5–2.5 group. Forty-five patients were in both groups. Twenty-three patients were in the RPA II group only (four were GPA 3.0–4.0 and 19 were GPA 0.5–1.0) and 16 patients were in the GPA 1.5–2.5 group only (seven were RPA I and nine were RPA III). The RPA II only and GPA 1.5–2.5 only groups were similar on age, sex, histology, number of fractions and surgery (all p > 0.2). Patients who were only in the RPA II group had significantly higher KPS scores than patients who were only in the GPA 1.5–2.5 group (mean KPS: 76.7 [±7.9] vs 65.9 [±14.5], two-sample *t*-test p = 0.0131). Also, a greater proportion of RPA II only patients had more than three CNS metastases compared with patients who were only in the GPA 1.5–2.5 group (60.9 vs 18.8%, Mantel-Haenszel χ^2 p = 0.0106).

On univariate analysis in the RPA II group, increased survival was associated with being younger, having better KPS, female, treated with >10 fractions and undergoing surgery/SRS. In the GPA 1.5–2.5 group, having better KPS, being treated with >10 fractions and undergoing surgery/SRS were associated with significantly longer survival **(Table 4)**.

Table 5. Recently published work concerning prognostic indices for brain metastases.

Study (year)	Patients included	Goal of study	Results	Ref.
Sperduto *et al.* (2012)	3940 patients	Concise update on the DS-GPA for easier clinical use	There is heterogeneity of prognosis that varies by primary tumor type	[28]
Sperduto *et al.* (2012)	400 patients with breast cancer primaries	Refine the breast DS-GPA by analyzing a larger cohort by tumor subtype	There is a wide variation in prognosis for breast tumor subtypes	[29]
Yamamoto *et al.* (2013)	4608 patients, Treated with GK	Comparing MS in the newly proposed Modified RPA-II to the DS-GPA for five histologies	Modified RPA-II is valid for all five histologies. The predicted MS differences were only valid with NSCLC primary in the DS-GPA index for this patient group	[32]
Yamamoto *et al.* (2012)	3753 patients treated with GK	Finding subclasses within the existing RPA-II group for better prognostic value	Created three subclasses within the RPA-II based on KPS, primary tumor control, number of brain mets, extra cranial mets	[14]
Serizawa *et al.* (2012)	2445 patients treated with GK	Comparing RPA, SIR, BSBM, GPA and Modified RPA-II for OS and QS	A better prognostic systems is needed for predicting QS	[27]
Bernholts-Slamen *et al.* (2012)	2367 patients from seven previous RTOG brain mets trials	Creating a new nomogram for prognosis	Index using primary histology, status of primary, extracranial mets, age, KPS and number of brain mets	[23]
Rodrigues *et al.* (2013)	501 patients treated with LINAC-based SRS or fractionated SRT	Comparing the usefulness of several validated indices using traditional and novel statistical metrics	RPA, GGS, RADES I and RDAM indices were superior in more than one metric. No index has clear superiority over RPA. GPA is the best for classifying poor prognosis	[26]
Viani *et al.* (2012)	412 patients treated with WBRT	Comparing GPA, RPA, BSBM, RDAM and Germany Score (RADES I) via a neural network	GPA is most powerful at predicting survival in the indices compared	[30]
Buglione *et al.* (2012)	382 patients treated with WBRT	Analyzing OS with the RPA index with respect to primary tumor histology	Primary histology is significant for OS in RPA I and II, but not III	[24]
Villa *et al.* (2011)	285 patients	Prospective analysis to validate the GPA	GPA is a valid index, as prognostic as RPA and BSBM	[31]
Likhacheva *et al.* (2012)	251 patients treated with SRS	Comparing RPA to the DS-GPA	DS-GPA is better for stratifying to treatment types	[25]

BSBM: Basic System for brain metastases; DS-GPA: Diagnosis specific-GPA; GGS: Golden grading system; GK: Gamma knife; GPA: Graded Prognostic Assessment; KPS: Karnofsky performance status; LINAC: Linear Accelerator; Mets: Metastases; MS: Median survival; NSCLC: Non-small-cell lung cancer; OS: Overall survival; QS: Quality of life survival; RADES I: Rades; *et al.* first index; RDAM: Rotterdam index; RPA: Recursive Partitioning Analysis; SIR: Score Index for Radiosurgery; SRS: Stereotactic radio surgery; SRT: Stereotactic radiation therapy; WBRT: Whole-brain radiation therapy.

Table 6. Comparison of prognostic indices used for survival in patients with brain metastases.

Index name	Characteristics included
RPA	KPS, age, controlled primary, extra cranial mets
GPA	KPS, age, number of brain mets, extra cranial mets
DS-GPA	Same as above but also considers primary histology
SIR	KPS, age, extra cranial mets, number of brain mets, largest brain met volume, site in brain, WBRT
BSBM	KPS, controlled primary, extra cranial mets
RADES-I	KPS, age, extra cranial mets, interval until WBRT
RDAM	KPS, response to steroids, systemic disease
GGS	KPS, age, extra cranial mets

BSBM: Basic System for Brain Metastases; DS-GPA: Diagnosis Specific-GPA; GGS: Golden Grading System; GPA: Graded Prognostic Assessment; KPS: Karnofsky performance status; Mets: Metastases; RADES I: Rades *et al.* first index; RDAM: Rotterdam index; RPA: Recursive Partitioning Analysis; SIR: Score Index for Radiosurgery; WBRT: Whole-brain radiation therapy.

On multivariable analysis among RPA II patients, receiving >10 fractions and undergoing surgery/SRS were significantly associated with increased survival. Patients receiving ≤10 fractions had an hazard ratio (HR) of 2.45 (95% CI: 1.35–4.44) with increased risk of death compared with patients receiving >10 fractions (p = 0.0033). Patients who did not undergo surgery/SRS had an HR of 4.76 (95% CI: 2.28–9.95) with increased risk of death compared with patients who did undergo surgery/SRS (p < 0.0001). Among patients with GPA 1.5–2.5, better KPS and undergoing surgery/SRS were significantly associated with increased survival on multivariable analysis. Every 5-point decrease in KPS was associated with an HR of 1.20 for an increase in risk of death (95% CI: 1.07–1.35; p = 0.0020). Patients who did not undergo surgery/SRS had an HR of 2.78 (95% CI: 1.44–5.35) with increased risk of death compared with patients who did undergo surgery/SRS (p = 0.0022). However, number of fractions received was not statistically significant in the final multivariable model for patients in the GPA 1.5–2.5 group. If number of fractions is included in the model, along with KPS and surgery/SRS, the hazard ratio is 1.63 (95% CI: 0.88–3.01; p = 0.1192).

Discussion

Our data show that all moderate prognosis patients who received surgery or SRS tended to have a survival advantage versus those who did not. This finding is well supported in the literature and is understood to be due more to patient selection than to the treatment choice [15–17].

Our analysis found that decreasing KPS was a hazard to survival for patients in the GPA 1.5–2.5 group, but not for patients in the RPA II group. This is likely because all patients in the RPA II category must have a relatively tight window of possible KPS values with a KPS ≥70. In the GPA 1.5 to 2.5 group KPS (a known independent predictor of survival) can be variable anywhere from 10 to 100 based on how the other three patient characteristics compromising the GPA are scored (Tables 1 & 2). Therefore, by definition of how the GPA is calculated, a continuum of patient outcomes in part related to the patient's KPS could be observed.

In the patients studied, RPA class and GPA scores were retrospectively assigned for this analysis. At the time of consultation, clinicians prescribed more or less aggressive WBRT fractionation schedules based on perceived prognosis. Patients assigned to the intermediate risk group with the RPA have a survival advantage with more aggressive WBRT fractionation (>10), but no such advantage was seen in the GPA intermediate risk group. As the number of treatment fractions should not be part of a prognostic system for estimating survival, this finding may indicate that the GPA is more helpful than the RPA for guiding clinicians' treatment decisions for moderate prognosis patients. There is perhaps too much variability in prognosis within the 'catch all' RPA II subgroup, leaving room for MS to be affected by more or less aggressive treatment decisions. The GPA is more granular by nature and does not seem to have this drawback.

Multiple prognostic indices exist for patients with brain metastases. We evaluated the RPA and the GPA, but some other commonly employed indices are: the DS-GPA, Score Index for Radiosurgery (SIR), Basic System for Brain Metastases (BSBM), RADES, Rotterdam score (RDAM) and Golden Grading System (GGS) [2,4,5,18–22]. Table 5 lists the factors considered when employing these prognostic guides.

The impetus for our study was our desire to help select the most appropriate treatment for our patients. Our dilemma was in selecting the most reliable, easy to use prognostic guideline. Several recent studies have been published with this same goal in mind **(Table 6)** [14,23–32].

The DS-GPA [28,29] has proved to be more granular than previous systems, but our population did not have enough patients of varying histologies to evaluate prognosis based on histology. A limitation of this study was a lack of power to find significance in survival between histologic subtypes, so in our analysis we chose to use the GPA as initially described. Although DS-GPA is the most recent system used for prognostication, the RPA and GPA are still being used in the radiation oncology and neuro-oncology communities. The GPA has also been validated to be a useful prognostic system [31] and compared with DS-GPA, the GPA is more user friendly. Future studies validating the DS-GPA against the GPA with larger groups of patients are warranted.

While our dataset is small and this is a single-institution retrospective study, our analysis contributes to the recently published body of work directed at finding a better prognostic definition for a sometimes difficult to assess population of patients. The volume of recent publications on this topic highlights the need among clinicians for better guidance when selecting treatment options for patients with metastatic brain disease when prognosis is unclear. Prospective studies are needed to better evaluate the ability of a prognostic index to guide treatment and accurately predict MS, quality of life and local control based on patient characteristics. Considering our results and our interpretation of the recent literature on this topic, the GPA (and, by extension, the DS-GPA) seems to be a reasonable prognostic index to bring forward into future prospective studies.

Conclusion

The objective of this study was to evaluate whether the GPA or the RPA provided more useful guidance to clinicians for estimating survival in patients with brain metastases who have moderate prognosis. Our analysis compares the two indices' moderate prognosis groups because optimal treatment for these patients (RPA II or GPA 1.5–2.5) can be unclear. Better prognosis patients are often prescribed longer schedules of whole brain radiation. The RPA II and GPA 1.5–2.5 have similar predicted median survivals (4.2 and 3.8 months), and in our patient group, those scored by the RPA and assigned a longer radiation schedule had a survival advantage, while patients scored by the GPA did not. When prognostic factors are 'treatment related,' such as we found in our analysis of the RPA II, further stratification within the prognostic tool could be difficult. This could also indicate that the GPA is more clinically useful because it does not have this drawback, therefore leaving less room for a clinician's subjective assessment in choosing treatment.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This retrospective research project was approved by our institutional review board.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 Klos KJ, O'Neill BP. Brain metastases. *Neurologist* 10(1), 31–46 (2004).

2 Gaspar L, Scott C, Rotman M *et al.* Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int. J. Radiat. Oncol. Biol. Phys.* 37(4), 745–751 (1997).

• **The original Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) was used for many years to guide treatment decisions.**

3 Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. *Int. J. Radiat. Oncol. Biol. Phys.* 47(4), 1001–1006 (2000).

4 Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int. J. Radiat. Oncol. Biol. Phys.* 70(2), 510–514 (2008).

- **The initial Graded Prognostic Assessment (GPA) system provided a more granular way to look at prognosis in patients with brain metastases.**

5 Sperduto PW, Chao ST, Sneed PK *et al.* Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. *Int. J. Radiat. Oncol. Biol. Phys.* 77(3), 655–661 (2010).

- •• **The diagnosis-specific GPA has further refined prognostic factors to allow prognosis based on primary tumor type in addition to patient characteristics.**

6 Chow E, Davis L, Holden L, Tsao M, Danjoux C. Prospective assessment of patient-rated symptoms following whole brain radiotherapy for brain metastases. *J. Pain Symptom Manage.* 30(1), 18–23 (2005).

7 Estabrook NC, Lutz ST, Johnson CS, Henderson MA. Whole brain radiotherapy for poor prognosis patients with brain metastases: predictably poor results. *J. Support. Oncol.* 11(4), 190–195 (2013).

8 Tsao MN, Rades D, Wirth A *et al.* Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. *Pract. Radiat. Oncol.* 2(3), 210–225 (2012).

9 Patchell RA, Tibbs PA, Walsh JW *et al.* A randomized trial of surgery in the treatment of single metastases to the brain. *N. Engl. J. Med.* 322(8), 494–500 (1990).

10 Andrews DW, Scott CB, Sperduto PW *et al.* Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 363(9422), 1665–1672 (2004).

11 Sahgal A, Aoyama H, Kocher M *et al.* Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int. J. Radiat. Oncol. Biol. Phys.* 91(4), 710–717 (2015).

12 Shaw EG, Gaspar LE, Gibbs FA *et al.* Multiple brain metastases. American College of Radiology. ACR Appropriateness Criteria. *Radiology* 215(8), 1121–1128 (2000).

13 Suh JH, Videtic GM, Aref AM *et al.* ACR Appropriateness Criteria: single brain metastasis. *Curr. Probl. Cancer* 34(3), 162–174 (2010).

14 Yamamoto M, Sato Y, Serizawa T *et al.* Subclassification of recursive partitioning analysis Class II patients with brain metastases treated radiosurgically. *Int. J. Radiat. Oncol. Biol. Phys.* 83(5), 1399–1405 (2012).

15 Mintz AH, Kestle J, Rathbone MP *et al.* A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 78(7), 1470–1476 (1996).

16 Posner JB. Management of brain metastases. *Rev. Neurol.* 148(6–7), 477–487 (1992).

17 Sause WT, Crowley JJ, Morantz R *et al.* Solitary brain metastasis: results of an RTOG/SWOG protocol evaluation surgery + RT versus RT alone. *Am. J. Clin. Oncol.* 13(5), 427–432 (1990).

18 Golden DW, Lamborn KR, Mcdermott MW *et al.* Prognostic factors and grading systems for overall survival in patients treated with radiosurgery for brain metastases: variation by primary site. *J. Neurosurg.* 109(12), (2008).

19 Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int. J. Radiat. Oncol. Biol. Phys.* 43(4), 795–803 (1999).

20 Lorenzoni J, Devriendt D, Massager N *et al.* Radiosurgery for treatment of brain metastases: estimation of patient eligibility using three stratification systems. *Int. J. Radiat. Oncol. Biol. Phys.* 60(1), 218–224 (2004).

21 Rades D, Dunst J, Schild SE. A new scoring system to predicting the survival of patients treated with whole-brain radiotherapy for brain metastases. *Strahlenther. Onkol.* 184(5), 251–255 (2008).

22 Weltman E, Salvajoli JV, Brandt RA *et al.* Radiosurgery for brain metastases: a score index for predicting prognosis. *Int. J. Radiat. Oncol. Biol. Phys.* 46(5), 1155–1161 (2000).

23 Barnholtz-Sloan JS, Yu C, Sloan AE *et al.* A nomogram for individualized estimation of survival among patients with brain metastasis. *Neuro Oncol.* 14(7), 910–918 (2012).

24 Buglione M, Bandera L, Grisanti S *et al.* The impact of tumour histology and recursive partitioning analysis classification on the prognosis of patients treated with whole-brain hypofractionated radiotherapy for brain metastases: analysis of 382 patients. *Radiol. Med.* 117(1), 133–147 (2012).

25 Likhacheva A, Pinnix CC, Parikh N *et al.* Validation of recursive partitioning analysis and diagnosis-specific graded prognostic assessment in patients treated initially with radiosurgery alone. *J. Neurosurg.* 117 38–44 (2012).

26 Rodrigues G, Gonzalez-Maldonado S, Bauman G, Senan S, Lagerwaard F. A statistical comparison of prognostic index systems for brain metastases after stereotactic radiosurgery or fractionated stereotactic radiation therapy. *Clin. Oncol.* 25(4), 227–235 (2013).

27 Serizawa T, Higuchi Y, Nagano O *et al.* Testing different brain metastasis grading systems in stereotactic radiosurgery: Radiation Therapy Oncology Group's RPA, SIR, BSBM, GPA, and modified RPA. *J. Neurosurg.* 117 31–37 (2012).

28 Sperduto PW, Kased N, Roberge D *et al.* Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J. Clin. Oncol.* 30(4), 419–425 (2012).

29 Sperduto PW, Kased N, Roberge D *et al.* Effect of tumor subtype on survival and the graded prognostic assessment for patients with breast cancer and brain metastases. *Int. J. Radiat. Oncol. Biol. Phys.* 82(5), 2111–2117 (2012).

30 Viani GA, Da Silva LG, Stefano EJ. Prognostic indexes for brain metastases: which is the most powerful? *Int. J. Radiat. Oncol. Biol. Phys.* 83(3), e325–e330 (2012).

31 Villa S, Weber DC, Moretones C *et al.* Validation of the new Graded Prognostic Assessment scale for brain metastases: a multicenter prospective study. *Radiat. Oncol.* 6(23), 6–23 (2011).

32 Yamamoto M, Serizawa T, Sato Y *et al.* Validity of two recently-proposed prognostic grading indices for lung, gastro-intestinal, breast and renal cell cancer patients with radiosurgically-treated brain metastases. *J. Neurooncol.* 111(3), 327–335 (2013).