Classification of Brain Metastases

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Introduction

Brain metastases are a common and complex conundrum for cancer care. An estimated 300,000 patients are diagnosed each year with brain metastases in the United States [1] and that incidence is growing due to advances in treatment that result in patients living longer and thus at prolonged risk for development of brain metastases [2]. It is a complex problem because of the marked heterogeneity of this patient population: brain metastases may arise from a wide variety of tumor types and subtypes. Furthermore, these patients may have already received a plethora of different treatments for their cancer or may present with brain metastases at the time of initial diagnosis. This heterogeneity has long plagued interpretation of clinical trials involving this patient population because it was essentially impossible to sufficiently stratify studies to verify similar groups of patients were being compared [3]. Interpretation of clinical trials and efforts to estimate prognosis are further complicated by the plethora of possible combinations of currently available treatment options [surgery, stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), chemotherapy, targeted drug therapies, and immunotherapies]. Furthermore, four prospective randomized trials have shown WBRT adds no survival benefit over SRS alone in SRS-eligible patients [4–7] and, on the other end of the prognostic spectrum, there is evidence that supportive care may be as effective as WBRT [8]. Accordingly, WBRT is used less commonly than in the past.

Classification Systems

These concerns led to efforts to better understand prognosis. The purpose of a prognostic index is to predict outcome before, not after, treatment. It is important to distinguish prognostic from predictive factors. A prognostic factor identifies good versus bad outcome irrespective of the treatment used, whereas a predictive factor identifies good versus bad outcome for a specific treatment. Gaspar et al. published the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis for brain metastases (Table 6.1) in 1997 [9]. This prognostic index consisted of three classes: I (age < 65, Karnofsky performance score (KPS) ≥70, controlled primary tumor, no extracranial metastases), II (all patients not in class I or III), and III (KPS < 70), which correlated with median survival of 7.7, 4.5, and 2.3 months, respectively, at that time. Weltman et al. published the score index for

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R. Ramakrishna et al. (eds.), *Central Nervous System Metastases*,
https://doi.org/10.1007/978-3-030-42958-4_6

Table 6.1 Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) for patients with brain metastases

Class	Criteria	Median survival
Class I	Age < 65 yrs, KPS ≥ 70, controlled primary tumor, and no extracranial metastases	7.1 mo
Class II	All patients not in Class I or III	4.2 mo
Class III	KPS < 70	2.1 mo

Data from Ref. [9]
KPS Karnofsky performance status

Table 6.2 Score index for radiosurgery (SIR)

	Score		
	0	1	2
Age (years)	≥60	51–59	≤50
KPS	≤50	60–70	80–100
Systemic disease	Progressive	Stable	CR or NED
Number of lesions	≥3	2	1
Volume of largest lesion (mL)	>13	5–13	<5

Data from Ref. [10]
Median survival (MS) by SIR score: SIR 1–3 (MS 2.91 mo), SIR 4–7 (MS 7.00 mo), SIR 8–10 (MS 31.38 mo)
KPS Karnofsky performance status, *CR* complete response, *NED* no evidence of disease

radiosurgery (SIR) (Table 6.2) in 2000 [10]. This index used the sum of scores (0–2) for each of five prognostic factors (age, KPS, status of systemic disease, number of brain metastases, and the volume of the largest metastasis). Lorenzoni et al. published the basic score for brain metastases (BSBM) (Table 6.3) in 2004 [11]. This index is based on the sum of scores (0–1) for three prognostic factors (KPS, control of primary tumor, and extracranial metastases). In 2012, Sloan-Barnholtz published a nomogram (Fig. 6.1) in an effort to further individualize prognosis [12]. In 2014, Kondziolka published an interesting survey study in which experts in the field were asked to estimate survival for a series of patients given all relevant clinical parameters. This study showed that even experts cannot predict outcomes with certainty for all patients [13]. All prognostic indices have limitations but can provide guidance for clinical decision-making and are essential for stratification of clinical trials so that those trials are comparing comparable

Table 6.3 Basic score for brain metastases (BSBM)

	Score	
	0	1
KPS	50–70	80–100
Control of primary tumor	No	Yes
Extracranial metastases	Yes	No

Data from Ref. [11]
Median survival (MS) by BSBM: BSBM 3 (MS >32 mo), BSBM 2 (MS 13.1 mo), BSBM 1 (MS 3.3 mo), BSBM 0 (MS 1.9 mo)
KPS Karnofsky performance status

patients, thus making the results of those trials worthwhile, relevant, and interpretable.

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 [14] based on 1960 patients from five randomized Radiation Therapy Oncology Group (RTOG) trials (7916, 8528, 8905, 9104, and 9508). Analysis showed four prognostic factors (age, KPS, extracranial metastases, and number of brain metastases) were significant for survival. Those prognostic factors were weighted in proportion to their regression coefficients and scaled such that patients with the best/worst prognosis would have a GPA of 4.0/0.0, respectively. In 2010, we refined the GPA based on an analysis of a retrospective multi-institutional database of 4259 patients. That study found survival varies by diagnosis and diagnosis-specific prognostic factors [15]. The Breast-GPA was then further refined using tumor subtype [16] and a summary report was published [17]. More recently, the GPA indices for lung cancer, melanoma, and renal cell carcinoma have been updated using molecular and other clinical factors with new data from patients (2,186 lung cancer and 823 melanoma patients) diagnosed since 2005 including molecular factors. The Lung-molGPA incorporates EGFR and ALK gene status [18, 19] and similarly the melanoma-molGPA incorporates *BRAF* status [20, 21]. The original melanoma-GPA found only two factors to be significant (KPS and the number of brain metastases), whereas the updated melanoma-molGPA found five factors (BRAF

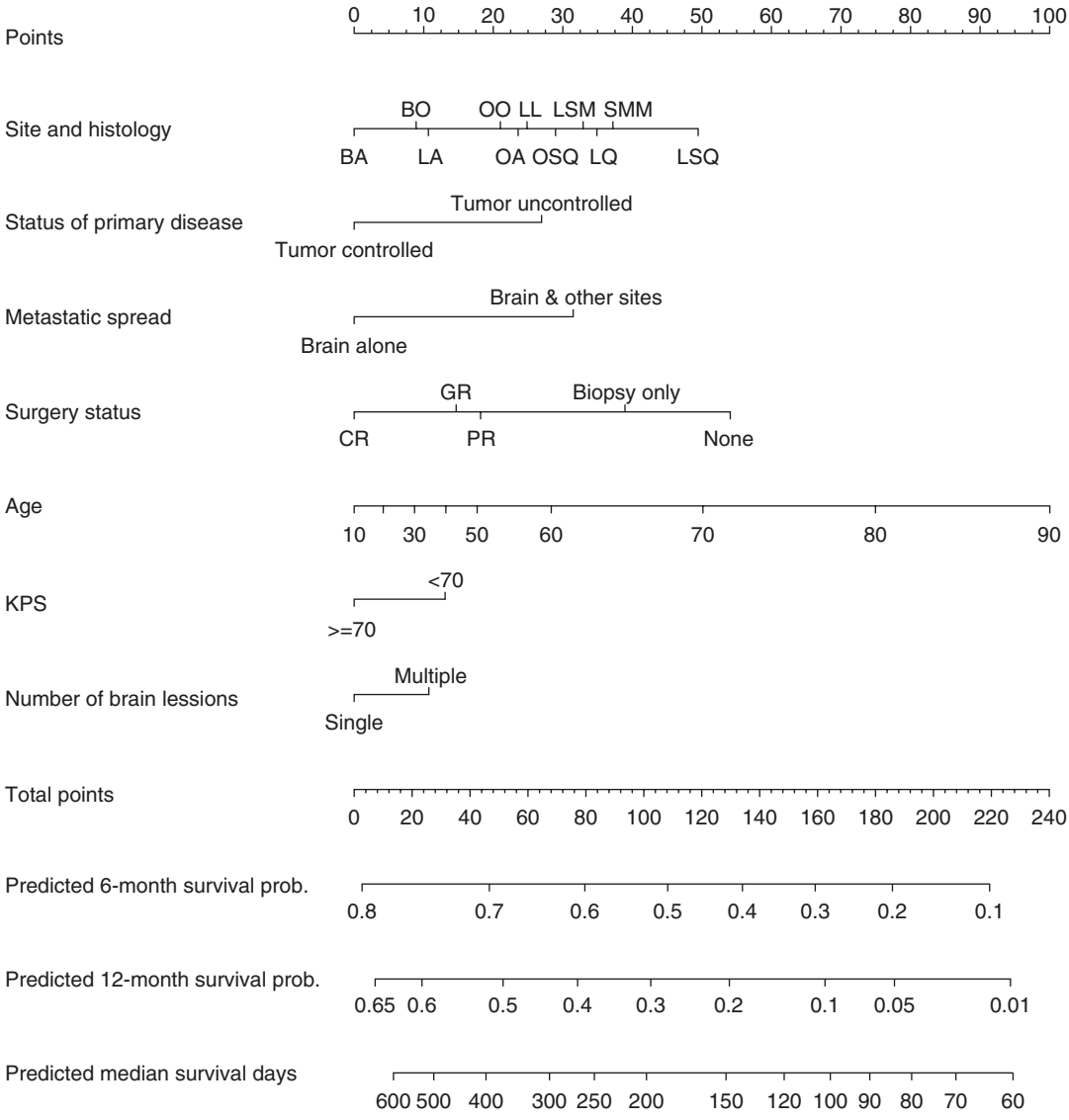

Fig. 6.1 Nomogram for 6-month and 12-month survival probability and median survival prediction for RTOG brain metastases patients. Abbreviations for site and histology: BA breast and adenocarcinoma, BO breast and other, LA lung and adenocarcinoma, LL lung and large cell, LO lung and other, LSM lung and small cell, LSQ lung and squamous cell, OA other and adenocarcinoma, OSQ other and squamous cell, SMM skin-melanoma, OO other and other. Surgery: PR partial resection, CR complete resection, GR gross resection. (Reprinted from Sloan-Barnholtz-Sloan et al. [12], with permission from Oxford University Press)

status, KPS, age, extracranial metastases, and number of brain metastases) to be significant. The renal GPA has also been updated. Data from 711 renal cell carcinoma patients with brain metastases, diagnosed between 2006 and 2016, showed four prognostic factors to be significant for survival: KPS, hemoglobin, extracranial metastases, and the number of brain metastases [22, 23].

Table 6.4 shows the median survival time for patients with brain metastases by diagnosis-specific GPA. Table 6.5 shows the diagnosis-specific definition of the updated GPA indices and a user-friendly worksheet to facilitate cal-

Table 6.4 Median survival time for patients with brain metastases by diagnosis specific—graded prognostic assessment score

		DS-GPA				
Diagnosis	Overall MST (95% CI) *N*	0–1.0 MST (95% CI) *n* (%)	1.5–2.0 MST (95% CI) *n* (%)	2.5–3.0 MST (95% CI) *n* (%)	3.5–4.0 MST (95% CI) *n* (%)	*p* (log-rank)
NSCLC	15 (14–17) 1521	7 (6–9) 337 (22%)	14 (12–15) 664 (44%)	26 (23–31) 455 (30%)	47 (37-NE) 65 (4%)	<0.001
SCLC	5 (4–6) 281	3 (2–3) 65 (23%)	5 (4–7) 119 (42%)	8 (6–9) 84 (30%)	17 (5–27) 13 (5%)	<0.001
Melanoma	10 (9–11) 823	5 (4–7) 136 (17%)	8 (7–9) 386 (47%)	16 (13–19) 256 (31%)	34 (24–50) 45 (5%)	<0.001
RCC	12 (11–13) 669	4 (3–5) 170 (25%)	12 (9–14) 178 (27%)	17 (13–21) 204 (30%)	35 (20–41) 117 (17%)	<0.001
Breast cancer	14 (12–16) 400	3 (3–4) 23 (6%)	8 (6–9) 104 (26%)	15 (13–16) 140 (35%)	25 (23–27) 133 (33%)	<0.001
GI cancer	5 (4–6) 209	3 (2–5) 76 (36%)	4 (3–7) 65 (31%)	7 (5–12) 50 (24%)	14 (10–27) 18 (9%)	<0.001
Other	6 (5–7) 450	–	–	–	–	–

The top row in each cell is the median survival time (MST) in months and its associated 95% CI. The bottom row is the frequency and percentage of patients with the corresponding DS-GPA category for a given diagnosis. Abbreviations: *DS-GPA* Diagnosis specific-graded prognostic assessment, *NSCLC* non-small cell lung cancer (adenocarcinoma), *SCLC* small cell lung cancer, *RCC* renal cell carcinoma, *GI* gastrointestinal, *NE* not estimable

Table 6.5 GPA worksheet to estimate survival from brain metastases by diagnosis

Non-small cell/small cell lung cancer	GPA scoring criteria				Patient
		0	0.5	1.0	Score
	Age	≥70	<70	n/a	–
	KPS	≤70	80	90–100	–
	ECM	Present		Absent	–
	#BM	>4	1–4	n/a	–
	Gene status	EGFR neg/unk and ALK neg/unk	n/a	EGFR pos or ALK pos	–
				Sum total =	–
Adenocarcinoma MS by GPA: GPA 0–1.0 = 6.9; 1.5–2.0 = 13.7; 2.5–3.0 = 26.5; 3.5–4.0 = 46.8					
Non-adenocarcinoma MS by GPA: GPA 0–1.0 = 5.3; 1.5–2.0 = 9.8; 2.5–3.0 = 12.8					
Melanoma		0	0.5	1.0	Score
	Age	≥70	<70	n/a	–
	KPS	<70	80	90–100	–
	ECM	Present	n/a	Absent	–
	#BM	>4	2–4	1	–
	Gene status	BRAF neg/unk	BRAF pos	n/a	–
				Sum total =	–
MS (mo) by GPA: 0–1.0 = 4.9, 1.5–2.0 = 8.3, 2.5–3.0 = 15.8, 3.5–4.0 = 34.1					

Breast cancer		0	0.5	1.0	1.5	2.0	Score
	KPS	≤50	60	70–80	90–100	n/a	–
	Subtype	Basal	n/a	LumA	HER2	LumB	–
	Age	≥60	<60	n/a	n/a	n/a	–
						Sum total =	–
Subtype:	Basal = triple negative (ER/PR/HER2-neg) LumA = Luminal A (ER/PR-pos, HER2-neg) LumB = Luminal B (triple positive, ER/PR/HER2-pos) HER2 = HER2-pos, ER/PR-neg						

Table 6.5 (continued)

Non-small cell/small cell lung cancer	GPA scoring criteria						Patient
MS (mo) by GPA: 0–1.0 = 3.4, 1.5–2.0 = 7.7, 2.5–3.0 = 15.1, 3.5–4.0 = 25.3							
Renal cell carcinoma			0	0.5	1.0	2.0	Score
	KPS		<80		80	90–100	–
	ECM		Present	Absent			–
	Hgb		≤11	11.1–12.5	>12.5		–
	#BM		>4	1–4			–
						Sum Total =	–
MS (mo) by GPA: 0–1.0 = 3.3, 1.5–2.0 = 7.3, 2.5–3.0 = 11.3, 3.5–4.0 = 14.8							
GI cancers		0	1	2	3	4	Score
	KPS	<70	70	80	90	100	–
MS (mo) by GPA: 0–1.0 = 3.1, 2.0 = 4.4, 3.0 = 6.9, 4.0 = 13.5							

Data from Refs. [17, 19, 21]

Abbreviations: *GPA* graded prognostic assessment, *KPS* Karnofsky performance score, *ECM* extracranial metastases, *#BM* number of brain metastases, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *MS* median survival in months, *neg/unk* negative or unknown

culation of the graded prognostic assessment by diagnosis and estimate survival for patients with brain metastases. A free online/smart phone application is available at brainmetgpa.com, which further simplifies the calculation of the GPA.

Table 6.6 shows a multivariate analysis of risk of death and median survival by treatment (excluding drug therapies) and diagnosis. It is important to understand these data are retrospective in nature with the selection bias inherent in all retrospective studies so one should not conclude that one treatment is better than another based on these data. Figure 6.2 shows Kaplan–Meier curves for survival for six diagnoses by GPA, demonstrating excellent separation between groups.

The diagnosis-specific GPA indices presented here define how survival has improved for brain metastasis patients over the past four decades. This progress mirrors the progress seen in survival for patients with the same diagnoses who do not have brain metastases. These data hold several implications for clinical management and research involving patients with brain metastases: (1) There is marked heterogeneity in outcomes for patients with brain metastases and these outcomes vary not only by diagnosis but also by diagnosis-specific prognostic factors, as detailed herein. Because of this heterogeneity, we should not treat all patients with brain metastases the same way—treatment should be individualized and the past philosophy of fatalistic futility should be abandoned. (2) On the other hand, as shown in Table 6.4, if a patient has a GPA of 0–1.0, regardless of diagnosis, their expected survival is poor. For these patients, supportive care, as suggested by the QUARTZ Trial [8], may be the best option. (3) For patients with GPA scores above 1.0, the median survival time (Table 6.4) varies more by diagnosis and more aggressive treatment strategies may be appropriate, but these retrospective data do not provide a basis for assuming that longer survival is a consequence of more aggressive treatment. Indeed, the survival by treatment data shown in Table 6.4 is certainly fraught with selection bias and should not be blindly applied or expected. Nonetheless, these data reflect patterns of care for patients with brain metastases. (4) Performance status is prognostic in every diagnosis. Clinicians should take the time to accurately assess and document their patients' performance status. (5) Table 6.5 shows the number of brain metastases is a significant prognostic factor for lung cancer, melanoma, and renal cell carcinoma, but not for breast or gastrointestinal cancers. Patients should not be denied treatment because of the number of brain metastases. (6) Extracranial metastases are only prognostic in lung cancer and melanoma but not in breast cancer, renal cell carcinoma, or gastrointestinal cancers. The implication here is that those patients with nonlung, nonmelanoma malignancies should not be denied aggressive

Table 6.6 Multivariable analysis of risk of death and median survival[a] by treatment and diagnosis

		Treatment					
		WBRT	SRS	WBRT + SRS	S + SRS	S + WBRT	S + WBRT + SRS
Diagnosis	Statistics						
NSCLC *n* = 1,521	Risk of death (HR)	1.0	1.08	1.20	0.66[b]	0.78	0.79
	95% CI		0.92–1.27	0.94–1.54	0.50–0.88	0.58–1.06	0.40–1.58
	p-value		0.35	0.15	<0.01	0.11	0.51
	Median survival[a]	13	14	10	32	20	20
	n (%)	342 (22%)	767 (50%)	139 (9%)	114 (7%)	76 (5%)	13 (1%)
SCLC *n* = 281	Risk of death (HR)	1.0	0.97	0.24[b]	0.00	0.42[b]	0.00
	95% CI		0.41–2.26	0.10–0.59	NA	0.25–0.73	NA
	p-value		0.94	0.002	0.99	0.002	0.98
	Median survival[a]	4	7	15	12	15	15
	n (%)	229 (81%)	13 (5%)	21 (7%)	1 (0.4%)	16 (6%)	1 (0.4%)
Melanoma *n* = 823	Risk of death (HR)	1.0	0.69[b]	0.62[b]	0.50[b]	0.54[b]	0.70
	95% CI		0.54–0.89	0.45–0.86	0.36–0.69	0.35–0.84	0.36–1.36
	p-value		< 0.01	<0.01	<0.01	<0.01	0.29
	Median survival[a]	6	10	9	13	11	11
	n (%)	91 (11%)	464 (56%)	73 (9%)	95 (12%)	34 (4%)	12 (1%)
Renal cell *n* = 711	Risk of death (HR)	1.00	0.84	0.78	0.38	0.64	1.29
	95% CI		0.62–1.12	0.51–1.19	0.25–0.59	0.38–1.08	0.45–3.68
	p-value		0.23	0.25	<0.01	0.09	0.64
	Median survival[a]	5	11	11	24	16	11
	n (%)	90 (12%)	410 (58%)	41 (6%)	70 (10%)	23 (3%)	4 (1%)
Breast cancer *n* = 400	Risk of death (HR)	1.0	1.07	0.74	0.59	0.72	0.47[b]
	95% CI		0.66–1.73	0.47–1.16	0.28–1.23	0.43–1.21	0.23–0.96
	p-value		0.80	0.18	0.16	0.72	0.04
	Median survival[a]	7	13	15	24	18	30
	n (%)	131 (33%)	115 (29%)	86 (22%)	19 (5%)	28 (7%)	20 (5%)
GI cancer *n* = 209	Risk of death (HR)	1.0	0.72	0.69	2.30	0.33[b]	0.39[b]
	95% CI		0.40–1.28	0.39–1.22	0.43–12.4	0.19–0.56	0.17–0.90
	p-value		0.26	0.21	0.33	<0.001	0.03
	Median survival[a]	3	7	7	9	10	8
	n (%)	95 (45%)	35 (17%)	35 (17%)	2 (1%)	34 (16%)	8 (4%)

Data from Refs. [17, 19, 21]

Diagnoses: *NSCLC* non-small-cell lung cancer (adenocarcinoma), *SCLC* small-cell lung cancer, *GI* gastrointestinal

Treatments: *S* surgery, *WBRT* whole brain radiation therapy, *SRS* stereotactic radiosurgery

Statistics: Risk of death: hazard ratio (HR) normalized to patients treated with whole brain radiation therapy alone (HR = 1.0) and calculated by multivariable Cox regression, adjusted for DS-GPA and stratified by institution

[a]Median survival in months based on one-sample Kaplan–Meier method

[b]Statistically significantly better than WBRT alone; 95% confidence interval

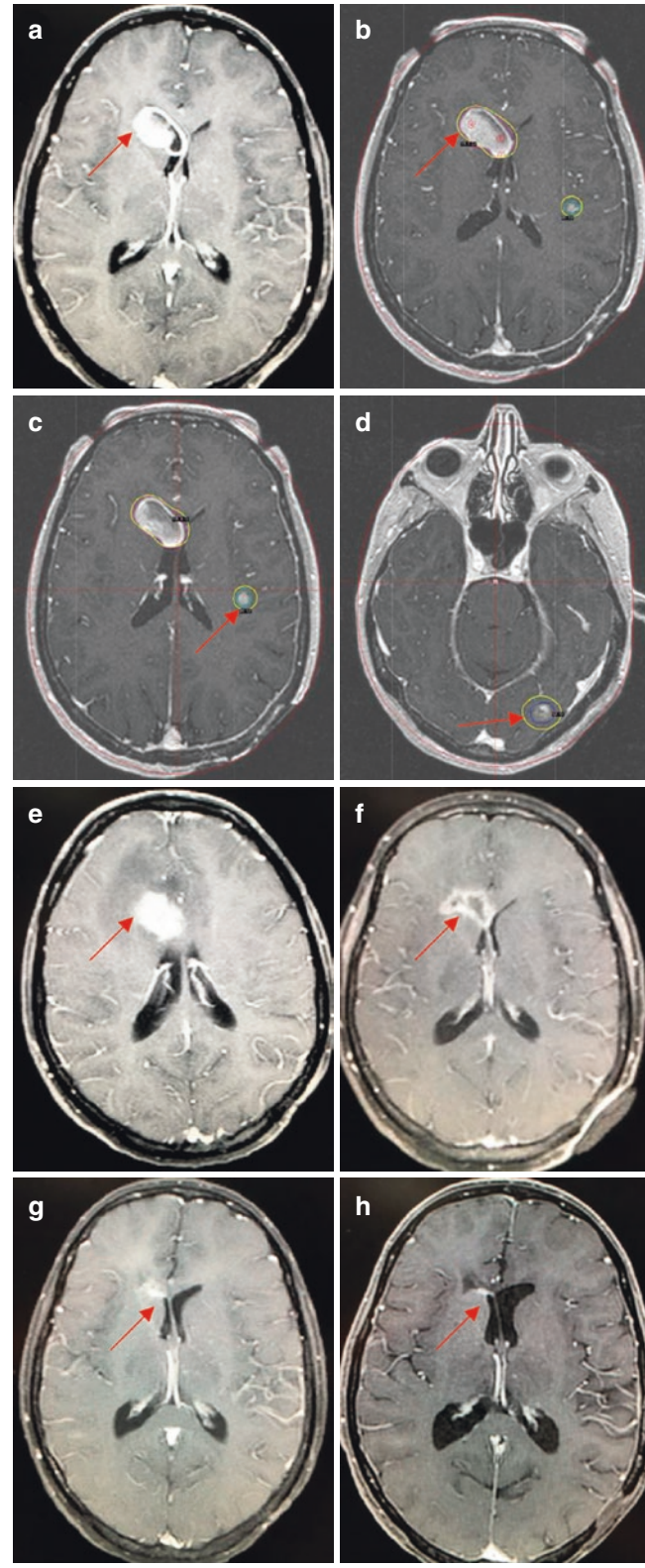

Fig. 6.2 Kaplan–Meier curves for survival by GPA for six diagnoses: breast cancer, non-–small-cell lung cancer, small-cell lung cancer, melanoma, renal cell carcinoma, gastrointestinal cancers. (**a**) Initial MRI shows largest of three brain metastases, December 06, 2006. (**b**) Gamma Knife plan for right frontal brain metastasis, December 13, 2006. (**c**) Gamma Knife plan for left frontal brain metastasis, December 13, 2006. (**d**) Gamma Knife plan for left occipital brain metastasis, December 13, 2006. (**e**) MRI 9 months after GK shows marked radiation necrosis and edema, September 26, 2007. (**f**) MRI 18 months after GK shows resolving radiation necrosis, May 23, 2008. (**g**) MRI 21 months after GK shows minimal residual enhancement, October 23, 2008. (**h**) MRI 10.7 years after GK shows no evidence of disease, August 02, 2017. (From Sperduto et al. [24]. Creative Commons Attribution License CC-BY 3.0)

treatment for their brain metastases because they have extracranial metastases. (7) Age is strongly prognostic in lung cancer and weakly prognostic in breast cancer and melanoma but not prognostic in renal cell carcinoma or gastrointestinal cancers. Thus, age should not be used as a rationale to withhold aggressive treatment for nonlung malignancies. (8) Because lung cancer and brain metastases from lung cancer are so common, those patients have masked our understanding of the distinct course for patients with nonlung malignancies and brain metastases, as demonstrated by points 5, 6, and 7 above. (9) Tumor subtype in breast cancer is of paramount importance and prognostic significance but it is not as prognostic as the Breast-GPA index. (10) A disproportionate number of patients with gastrointestinal cancers present with GPA of 0–1.0. Whether this is due to lack of screening MRI in these patients versus other biological reasons remains unclear but the finding should serve as a reminder that brain metastases are not uncommon in GI cancer patients. On-going research will better elucidate prognosis for these patients and the GI-GPA will be updated accordingly. (11) Clinicians may use the worksheet in Table 6.5 or go to brainmetgpa.com, a free user-friendly smart-phone application to calculate their patient's GPA score and estimate survival [12]. The GPA may be used for purposes of stratification in clinical trials dealing with patients with brain metastases.

All prognostic indices are imperfect and cannot always predict the outcome for an individual patient. The following case study is remarkable for the patient's outcome because it demonstrates not only the application of the GPA in a clinical setting but also the potential pitfalls of prognostic indices for such a heterogeneous patient population.

Case Study

A 36-year-old white female marathon runner presented in August 2005 with a right neck mass. Fine needle aspiration initially confirmed a malignancy, later confirmed as a malignant melanoma by excisional biopsy of a posterior scalp lesion on September 15, 2005. This malignant melanoma was histopathologically staged as Clark's Level IV, Breslow depth at least 6 mm, with angiolymphatic invasion and positive deep and peripheral margins. Brain MRI for initial radiologic staging on September 27, 2005, showed multiple scalp lesions but no evidence of parenchymal brain metastases. PET scan on September 27, 2005, showed hypermetabolic activity only in the left neck. On October 11, 2005, she underwent a left modified radical neck dissection and wide local excision of the scalp lesion. Pathology confirmed metastatic melanoma in 3 of 28 lymph nodes with extension into the adjacent soft tissues in two areas. Pathology from the scalp excision showed a maximum tumor depth of 1.9 cm and the deep margin remained positive. She underwent two additional scalp excisions and the deep margin remained positive. Her stage was T4bN2bM0, stage IIIC. She received 64 Gy radiation therapy to the left neck and scalp, completed on January 20, 2006. She then received three cycles of cisplatinum, interferon, and vinblastine followed by interleukin-2, completed in March 2006. She did well without evidence of recurrence until November 2006 when she underwent a debridement of necrotic tissue in the scalp lesion. PET scan on December 5, 2006, showed a 0.7 cm hypermetabolic nodule in the retroperitoneum consistent with metastatic recurrence. Brain MRI on December 6, 2006, showed three brain metastases (2.5 cm right caudate, 1.1 cm left parieto-occipital, and 0.7 cm left posterior frontal) (Fig. 6.2a), which were not present on the prior scan performed on June 22, 2006.

Whole brain radiation therapy was not given (and has not been given) due to the prior scalp radiation. She underwent SRS (Gamma Knife) on December 13, 2006, to all three lesions: right caudate, 20 Gy to a volume 8.4 cm^3 (Fig. 6.2b); left posterior frontal 24 Gy to a volume of 0.47 cm^3 (Fig. 6.2c); and left parieto-occipital, 24 Gy to a volume of 1.6 cm^3 (Fig. 6.2d). She underwent SABR to the pelvic soft tissue metastasis (25 Gy × 5 over two weeks, completed

on February 23, 2007). Between March and June 2007, she received four cycles of carboplatin, paclitaxel, and temozolomide treatment. In September 2007, she developed headaches, nausea, vomiting, and confusion. MRI on September 26, 2007, showed a marked increase in enhancement and edema in the right frontal lobe consistent with radiation necrosis (Fig. 6.2e). Due to increased headaches and possible radiation necrosis, the temozolomide was discontinued. She has received no treatment since September 2007. The edema was treated with steroids, which were gradually tapered off over four months. Brain MRI on May 23, 2008, showed improvement with central necrosis of the previously solid-appearing lesion (Fig. 6.2f). Brain MRI on October 23, 2008, showed further resolution of the enhancement/necrosis with minimal residual enhancement (Fig. 6.2g). Serial imaging since that time has shown no evidence of recurrent tumor or necrosis.

She remains clinically and radiographically free of disease 13 years after the diagnosis of multiple brain metastases and more than 10 years after completion of treatment. Brain MRI on August 2, 2017, showed no change in the minimal residual enhancement/scar tissue (Fig. 6.2h) and PET scan on August 2, 2017, showed no evidence of disease. She has remained asymptomatic for over a decade and continues to run marathons, as recently as October 14, 2017. In November 2017, she completed the FACT-Brain questionnaire, a patient-reported QOL tool to reassess brain cognition. Her FACT-BR score was perfect (200 on a scale of 200), 11 years after diagnosis of her brain metastases. Notably, this patient never underwent craniotomy or whole brain radiation therapy and thus avoided the related long-term neurocognitive toxicity of these interventions.

To fully appreciate this patient's remarkable outcome, it is appropriate to review how her outcome compares to the best available evidence of survival for melanoma patients with brain metastases. We recently updated and published the melanoma-molGPA [20, 21] based on a multi-institutional retrospective study of 483 melanoma patients with brain metastases diagnosed between January 1, 2006, and December 31, 2015. Notably, the patient presented here was diagnosed in 2006, so she is a contemporary of the patients in the melanoma-molGPA update study. The study showed five prognostic factors significant for survival (Table 6.5).

Overall median survival for melanoma patients with brain metastases has improved from 6 to 10 months since the 1980s, and the median survival by melanoma-molGPA groups for GPA of 0–1.0, 1.5–2.0, 2.5–3.0, and 3.5–4.0 was 4.9, 8.3, 15.8, and 34.1 months, respectively. The patient presented here had a melanoma-GPA of 3.0 on a 4.0 scale on both the original and updated GPA indices, correlating with an estimated survival of 8.8 and 15.8 months, respectively. This patient is disease-free and asymptomatic with a perfect FACT-Brain QOL score 13 years after the diagnosis of multiple brain metastases. Clearly, prognostic indices are imperfect but nonetheless provide our best estimate of survival for these patients.

Summary

Patients with brain metastases are a heterogeneous population and outcomes vary widely by diagnosis and diagnosis-specific prognostic factors. Because of this heterogeneity and the plethora of available treatment options, it is difficult to estimate survival. These problems have complicated clinical decision-making as well as interpretation of clinical trials. The graded prognostic assessment (GPA) is a diagnosis-specific prognostic index that has been updated to reflect the current treatment era by incorporating diagnosis-specific prognostic factors including molecular factors such as tumor subtype and gene status. The GPA is useful for clinical decision-making as physicians determine whether and what treatment is appropriate for these patients. It can also be useful to stratify clinical trials to ensure those trials are comparing comparable patients, which is especially important in such a heterogeneous patient population. Without accurate stratification, the results of clinical trials are uninterpretable and a waste of resources.

Acknowledgments This work has been a collaborative multi-institutional effort. The faculty and residents of the following institutions have selflessly contributed time and energy to one or more of the studies on the graded prognostic Assessment: MD Anderson, Memorial Sloan Kettering Cancer Center, Mayo Clinic, University of California San Francisco, Mayo Clinic, Massachusetts General Hospital, Dana Farber Cancer Institute, Duke University, Yale University, University of Colorado Denver, Cleveland Clinic, University of Wisconsin Madison, McGill University and Centre Hospitalier de l' Université de Montreal, University of Maryland, University of Alabama Birmingham, and the University of Minnesota. This work would not have been possible without the tireless work of these dedicated colleagues. Special recognition is appropriate for Ryan Shanley who has provided his statistical wisdom for nearly a decade.

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