Identifying Better Surgical Candidates Among Recursive Partitioning Analysis Class 2 Patients who Underwent Surgery for Intracranial Metastases

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Key words
- Breast
- Gastrointestinal
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- RPA
- Surgery
- Survival

Abbreviations and Acronyms
CI: Confidence interval
GPA: Graded prognostic assessment
GTR: Gross total resection
IQR: Interquartile range
KPS: Karnofsky performance score
MRI: Magnetic resonance imaging
NSCLC: Non-small cell lung cancer
RPA: Recursive partitioning analysis
RR: Relative risk
SRS: Stereotactic radiosurgery
WBRT: Whole brain radiation therapy

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■ OBJECTIVE: **The management of patients with brain metastases is typically dependent on their prognosis. Recursive partitioning analysis (RPA) is the most commonly used method for prognosticating survival, but has limitations for patients in the intermediate class. The aims of this study were to ascertain preoperative risk factors associated with survival, develop a preoperative prognostic grading system, and evaluate the utility of this system in predicting survival for RPA class 2 patients.**

■ METHODS: **Adult patient who underwent intracranial metastatic tumor surgery at an academic tertiary care institution from 1997 to 2011 were retrospectively reviewed. Multivariate proportional hazards regression analysis was used to identify preoperative factors associated with survival. The identified associations were then used to develop a grading system. Survival as a function of time was plotted using the Kaplan-Meier method, and survival rates were compared using log-rank analyses.**

■ RESULTS: **A total of 421 (59%) of 708 patients were RPA class 2. The preoperative factors found to be associated with poorer survival were: male gender ($P < 0.0001$), motor deficit ($P = 0.0007$), cognitive deficit ($P = 0.0004$), nonsolitary metastases ($P = 0.002$), and tumor size >2 cm ($P = 0.003$). Patients having 0–1, 2, and 3–5 of these variables were assigned a preoperative grade of A, B, and C, respectively. Patients with a preoperative grade of A, B, and C had a median survival of 17.0, 10.3, and 7.3 months, respectively. These grades had distinct survival times ($P < 0.05$).**

■ CONCLUSIONS: **The present study devised a preoperative grading system that may provide prognostic information for RPA class 2 patients, which may also guide medical and surgical therapies before any intervention is pursued.**

INTRODUCTION

An estimated 25%–45% of patients with cancer will develop brain metastases (10, 12). The management of patients who develop brain metastases includes some combination of surgery, radiation therapy, and/or chemotherapy (3, 10-13). The choice of therapies primarily depends on an estimation of a patient's individual survival, where patients with better prognoses are typically offered more aggressive therapies (3, 10-13). The most commonly used method for predicting an individual's prognosis is the recursive partitioning analysis (RPA) classification system (3). This three-tiered system is based on age, Karnfosky performance score (KPS), primary tumor control, and presence of extracranial disease (3, 15, 16, 25, 26, 35). RPA class 1 patients have the best prognoses, and are therefore typically offered surgery and other aggressive therapies (10, 12). RPA class 3 patients have the worst prognoses, and are generally only offered salvage therapies (10, 12). However, the optimal treatment regimen for RPA class 2 patients, which is the largest group of patients with metastatic disease, is poorly defined (10, 12).

Several studies have attempted to identify factors associated with prognosis for patients who undergo surgery for intracranial metastases (19, 23, 24, 27, 29, 33, 34). These studies, however, are limited in prognosticating outcomes for RPA class 2 patients because they include RPA class 1 and 3 patients, patients who did not undergo surgery, and patients with only solitary metastases, among others (19, 23, 24, 27, 29, 33, 34). The surgical outcomes for RPA class 2 patients and the factors associated with better or worse outcomes after surgery remains unclear. Therefore, the goals of this study were to: 1) ascertain additional preoperative risk factors associated with survival; 2) develop a preoperative prognostic classification system; and 3) evaluate the utility of this classification system in predicting survival for RPA class 2 patients undergoing intracranial surgery. This understanding may better help define which RPA class 2 patients benefit the most from surgical therapy. This is important as RPA class 2 patients represent the largest and also the most controversial group of patients with metastatic disease.

METHODS

Patient Selection

Institutional Review Board approval (36875) was obtained before the start of this study. All adult patients (aged >18 years) who underwent needle biopsy and/or surgical resection of a single or multiple intracranial metastases between 1997 and 2011 were retrospectively reviewed (Figure 1). RPA class 2 patients who did not undergo surgery were not available for review. The pathology was determined by a senior neuropathologist in all cases. RPA classification group was assigned to each of these patients based on the clinic note before surgery by a clinician blinded to patient outcomes, as previously described (15). Patients with a preoperative RPA class 2 were included in the study. This included patients older than 65 years, KPS ≥70, presence or absence of primary tumor control, and presence or absence of extracranial disease (15). According to this classification scheme, primary tumor control refers to control of the primary tumor at the primary site, whereas extracranial disease was the presence of metastases in addition to the brain metastases (15). Patients whose RPA class was difficult to determine were excluded.

Recorded Variables

The neurosurgery and neuro-oncology clinical notes for all patients who met the inclusion criteria were reviewed. The information collected included patient demographics, comorbidities, presenting symptoms, brain and body imaging characteristics, postoperative neurological function, and use of adjuvant therapies. A KPS index score was assigned to each patient based on the clinic note before surgery (9). A motor deficit was defined as any decrease in strength, a language deficit as any difficulty in producing and/or understanding speech, a cognitive deficit as any decrease in mental status or ability, and a visual deficit as any decrease in visual acuity or peripheral field perception.

All patients underwent preoperative and postoperative magnetic resonance imaging (MRI) with and without gadolinium. The characteristics that were recorded included the lesion's size (largest diameter based on gadolinium enhancement), specific lobe involvement, number of intracranial metastases, and extent of resection. Extent of resection was determined by comparing preoperative and postoperative MRIs obtained <48 hours after surgery. Gross total (GTR), near total, and subtotal resection were defined if 100%, 95%—100%, and <95% resection was seen on postoperative MRI, respectively (22). All patients underwent computed tomography scans of the chest, abdomen, pelvis, and spine with oral and intravenous contrast to identify control of primary tumor and presence of extracranial spread. These whole body scans were typically done within 1 week of surgery to stage the patient's tumor burden.

The Social Security index database was used to used to determine patients' survival times (1). Survival time was calculated from time of surgery to death. Patients whose deaths were unconfirmed with the use of the Social Security index database were classified as lost to follow-up at the time of the last clinic visit.

General Treatment Strategy

Surgery was generally advocated for patients who presented with intracranial metastases without a diagnosis or for lesions causing symptoms due to location or swelling. The general goal was to achieve GTR of the tumor when not involving eloquent locations. Surgery was pursued for multiple metastases when the metastases were easily accessible and/or causing symptoms. Motor and somatosensory evoked potentials were used in most patients, whereas surgical navigation (computed tomography and/or MRI wand) was used in all cases after 2001.

Postoperative MRI with gadolinium was typically performed at 3-month intervals after surgery, or when symptoms developed. Adjuvant therapy, including radiation and chemotherapy, was determined by a tumor board consisting of a multidisciplinary team comprised of members from neurosurgery, neuro-oncology, medical oncology, and radiation oncology, as well as the patients and their families.

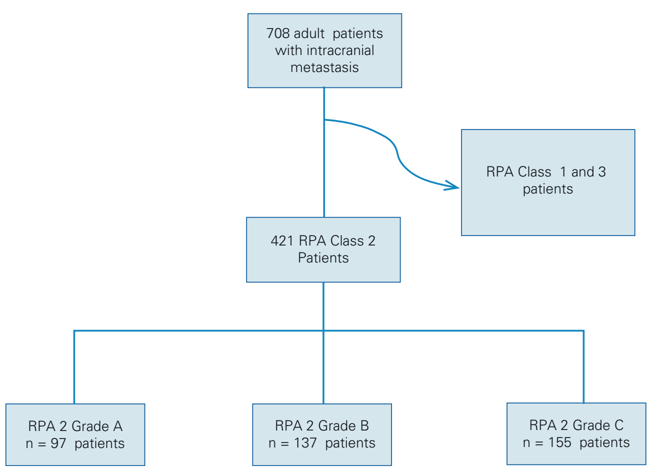

Figure 1. Schematic diagram of the study. All patients who underwent surgery for an intracranial metastasis were reviewed. All patients with a preoperative recursive partitioning analysis (RPA) class 2 were then included in the study (421 patients). Of these 421 patients, 97 patients had an RPA class 2 grade A, 137 patients had an RPA class 2 grade B, and 155 patients had an RPA class 2 grade C. Thirty-two patients were excluded because they did not have sufficient preoperative information to assign grade.

Statistical Analysis

Summary data were presented as mean ± standard deviation and median (interquartile range [IQR]) for parametric and nonparametric data, respectively. Intergroup comparisons were made using Student's *t*-test for continuous data and Fisher's exact test for categorical data. Stepwise multivariate proportional hazards regression analysis was used to identify independent factors associated with overall survival. In this analysis, univariate analyses were first performed to identify potential factors associated with survival. Factors with $P < 0.10$ were included into a stepwise multivariate proportional hazards regression analysis. Survival as a function of time was plotted using the Kaplan-Meier method, and log-rank analysis was used to compare Kaplan-Meier plots (GraphPad Prism 5, La Jolla, California, USA). Values with $P < 0.05$ in these analyses were considered statistically significant. JMP 9 (SAS, Cary, North Carolina, USA) was used unless otherwise specified.

RESULTS

Preoperative Characteristics of all RPA Class 2 Patients

The preoperative characteristics of the 421 adult patients in this study are summarized in Table 1. Of the 708 patients who underwent surgery for an intracranial metastasis, 421 (59%) presented with a preoperative RPA class 2. The average age of these RPA class 2 patients was 59.6 ± 13.1 years, and 199 (47%) of these patients were men. The mean presenting KPS was 80.9 ± 8.3. The most common presenting symptoms in this cohort were headaches in 162 (38%), motor deficit in 134 (32%), visual deficit in 79 (19%), cognitive deficit in 62 (15%), and seizures in 61 (14%).

The most common primary tumor among the RPA class 2 patients was non-small cell lung cancer (NSCLC) in 143 (34%), breast cancer in 67 (16%), melanoma in 56 (13%), and gastrointestinal cancer in 43 (10%). Two hundred fifty-eight (61%) had primary tumor control at the time of surgery, whereas 266 (63%) had extracranial spread of their primary tumor. The median [IQR] number of metastatic sites were 2 [1–3].

Table 1. Preoperative, Perioperative, and Postoperative Characteristics of Recursive Partitioning Analysis Class 2 Patients Undergoing Surgery for Intracranial Metastases From 1997 to 2001 at a Single, Tertiary Care Institution (Study Population n = 421)

Characteristics	Number (%)
Gender	
Male	199 (47)
Age*	59.6 ± 13.1
Presenting symptoms	
KPS*	80.9 ± 8.3
Preoperative symptoms	
Seizures	61 (14)
Headaches	162 (38)
Motor deficit	134 (32)
Sensory deficit	45 (11)
Language deficit	59 (14)
Visual deficit	79 (19)
Cognitive deficit	62 (15)
Primary tumor	
NSCLC	143 (34)
Breast	67 (16)
Gastrointestinal	43 (10)
Melanoma	56 (13)
Renal	38 (9)
Bone	11 (3)
Other	63 (15)
Primary tumor control	258 (61)
Extracranial spread	266 (63)
Radiographics:	
Tumor size (cm)*	3.2 ± 1.4
Location	
Frontal	148 (35)
Temporal	62 (15)
Parietal	93 (22)
Occipital	62 (15)
Skull base	13 (3)
Bone involvement	29 (7)
Eloquent regions	89 (21)
Posterior fossa	91 (22)
Number of intracranial metastases†	1 (1–2)
Solitary metastasis	284 (67)
Hemorrhagic	78 (19)
Periventricular	99 (24)
Metastatic sites†	2 (1–3)
Surgical variables	
Gross total resection	298 (71)
Near total resection	82 (19)
Subtotal resection	41 (10)
Perioperative outcomes	
Iatrogenic deficit	
New motor deficit	35 (8)
New language deficit	15 (4)
New visual deficit	9 (2)
Surgical site infection	8 (2)
Medical complication	
DVT/PE	21 (5)
Pneumonia	2 (0.5)
MI	1 (0.2)
Discharge to home	323 (77)
Adjuvant therapy	
Chemotherapy	173 (41)
Any brain radiation therapy	281 (67)
Whole brain radiation	215 (51)
Stereotactic radiosurgery	139 (33)
Survival	
Died at last follow-up	324 (77)
Follow-up (months) for nondeceased patients†	7.3 (2.2–22)
Median survival (months)	9.6
6-month survival rate	62.4%
12-month survival rate	42.4%
18-month survival rate	31.2%
24-month survival rate	25.9%

NSCLC, non-small cell lung cancer; DVT/PE, deep vein thrombosis/pulmonary embolism; MI, myocardial infarction.
*Mean ± standard deviation.
†Median (interquartile range).

With regard to their intracranial metastasis, the average operated tumor size was 3.2 ± 1.4 cm, and 148 (35%) involved the frontal lobe, 62 (15%) the temporal lobe, 93 (22%) the parietal lobe, 62 (15%) the occipital lobe, and 91 (22%) the cerebellum. The median [IQR] number of intracranial metastases was 1 [1–2], and 284 (67%) had solitary metastasis.

Perioperative and Postoperative Outcomes of all Patients

The perioperative and postoperative outcomes are also summarized in Table 1. Forty-eight (11%) patients underwent resection of multiple intracranial metastases. GTR of the resected lesions was achieved in 298 (71%), near total resection in 82 (19%), and subtotal resection in 41 (10%). Perioperatively, 35 (8%), 15 (4%), and 9 (2%) developed a new motor, language, and visual deficit, respectively. Eight patients (2%) incurred a surgical site infection, and 5 (1%) had an intracranial hemorrhage requiring operative evacuation. At last follow-up, 173 (41%) received postoperative chemotherapy, and 281 (67%) underwent radiation therapy. Among those who underwent radiation therapy, 51% underwent whole brain therapy (WBRT) and 33% underwent stereotactic radiosurgery (SRS). Among the patients who underwent SRS, 96 (69%) and 56 (40%) underwent SRS to the resected tumor bed and/or other brain metastases.

Three hundred twenty-four patients (77%) had died at last follow-up. Of the patients who died, the cause of death could be ascertained in 201 patients (62%). Of these 201 patients, 137 (68%) died of progressive systemic cancer, 37 (18%) died of progressive central nervous system disease, and 27 (13%) died of a medical complication (i.e., pneumonia, myocardial infarct, pulmonary embolism). The median survival of these patients was 9.6 months, where the 6-, 12-, and 24-month survival rates of 62%, 42%, and 26% respectively (Figure 2). The median [IQR] follow-up time for surviving patients was 7.3 [2.2–21] months. Local recurrence occurred in 59 (14%), where the 12-, 24-, 36-, and 48-month local progression-free survival rates were 80%, 73%, 63%, and 63%, respectively. Distal intracranial recurrence occurred in 150 (36%). The median time to distal recurrence was 14.8 months, where the 6-, 12-, 24-, 36-, and 48-month distal progression-free survival rates were 72%, 54%, 39%, 27%, and 26%, respectively.

Preoperative and Perioperative Factors Independently Associated with Survival for RPA Class 2 Patients with Intracranial Metastases

In univariate proportional hazards regression analyses, the factors associated with survival were age, male gender, diabetes, hypertension, headaches, motor deficit, cognitive deficits, colon cancer, liver cancer, renal cell cancer, extracranial spread, skull base metastasis, solitary metastasis, tumor size, new neurological deficit, hospital stay, discharge to rehabilitation, postoperative chemotherapy, and postoperative radiation therapy. No other clinical or radiographic factors were associated with survival in univariate analyses including primary tumor control, extent of resection, number of metastatic sites, and SRS.

In stepwise multivariate proportional hazards regression analysis, the preoperative factors that remained significantly associated with *poorer* survival were male gender (relative risk [RR], 1.687; 95% confidence interval [CI] 1.322–2.155; $P < 0.0001$), preoperative motor deficit (RR, 1.564; 95% CI 1.209–2.011; $P = 0.0007$), preoperative cognitive deficit (RR, 1.797; 95% CI 1.309–2.426; $P = 0.0004$), nonsolitary metastasis (RR, 1.504; 95% CI 1.160–1.939; $P = 0.002$), and increasing tumor size (RR, 1.098; 95% CI 1.015–1.185; $P = 0.02$) (Table 2). This was done with controlling for perioperative factors found to be associated with survival (new neurological deficit, discharge to rehabilitation, and no radiation therapy). In a separate analysis to find the tumor size most significantly associated with *poorer* survival, tumor size was dichotomized in centimeter intervals. Tumor size >2 cm (RR, 1.654; 95% CI 1.253–2.211; $P = 0.003$) had the greatest statistical association with poor outcome in multivariate analysis.

Because male gender was independently associated with worsened survival, male and female patients were compared with regard to preoperative, perioperative, and postoperative factors. Male patients were older (62.3 ± 12.4 vs. 57.2 ± 13.0 years; $P = 0.0001$); more commonly had NSCLC (41% vs. 28%; $P = 0.007$), melanoma (19% vs. 9%; $P = 0.03$), and renal cell cancer (14% vs. 5%; $P = 0.002$); less commonly breast cancer (37% vs. 0; $P < 0.0001$); less commonly extracranial spread (53% vs. 72%; $P = 0.0001$); and more commonly had solitary metastasis (74% vs. 61%; $P = 0.007$). Men and women did not differ in other preoperative, perioperative, and postoperative characteristics. In multivariate analysis, after controlling for these differences, male

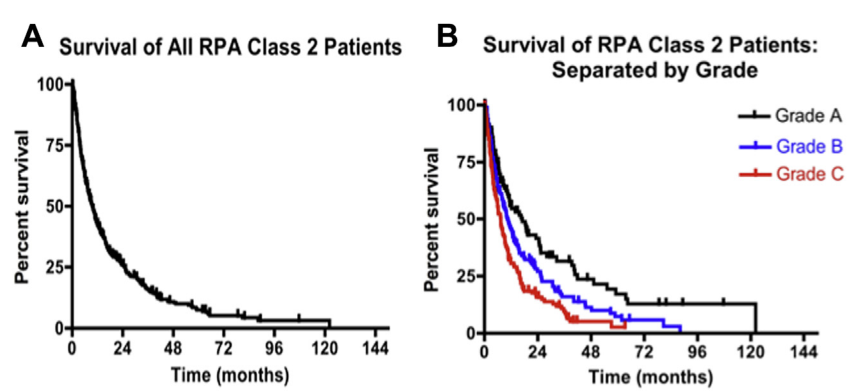

Figure 2. Survival for recursive partitioning analysis (RPA) class 2 patients in this study. **(A)** Kaplan-Meier survival curves for all RPA class 2 patients undergoing surgery for intracranial metastases from 1997 to 2011. The median survival was 9.6 months, where the 6-, 12-, 24-, and 36-month survival rates were 62.4%, 42.4%, 25.9%, and 15.9%, respectively. **(B)** Kaplan-Meier survival curves for all RPA class 2 patients divided by grade. In multivariate analyses, male gender, motor deficit, cognitive deficit, tumor size >2 cm, and nonsolitary metastasis were found to be independently associated with survival. Patients with 0–1, 2, and 3–5 of these factors were assigned a grade of A, B, and C, respectively. The median survival for patients with a grade A was 17 months, grade B was 10.3 months, and grade C was 7.3 months. RPA class 2 patients with a preoperative grade A had a significantly longer survival than grade B ($P = 0.01$) and C ($P < 0.0001$) patients. Likewise, patients with a preoperative grade B had a significantly longer survival than grade C patients ($P = 0.009$).

Table 2. Multivariate Associations of Preoperative Variables with Survival for Recursive Partitioning Analysis Class 2 Patients Undergoing Surgery for Intracranial Metastases From 1997 to 2011 at a Single, Tertiary Care Institution

Multivariate Associations with Survival

Variables	Hazards Ratio (95%CI)	*P* Value
Preoperative factors associated with poorer survival		
Male	1.687 (1.322–2.155)	< 0.0001
Motor deficit	1.564 (1.209–2.011)	0.0007
Cognitive deficit	1.797 (1.309–2.426)	0.0004
Nonsolitary metastases	1.504 (1.160–1.939)	0.002
Tumor size	1.098 (1.015–1.185)	0.02
Tumor size >2 cm*	1.654 (1.253–2.211)	0.003
Factors notably not associated with survival		
Age†	1.001 (0.991–1.011)	0.82
KPS	1.000 (0.987–1.013)	0.99
Melanoma	1.095 (0.788–1.486)	0.58
Renal cell cancer	0.760 (0.504–1.099)	0.15
NSCLC	1.097 (0.871–1.376)	0.43
Breast cancer	0.834 (0.605–1.125)	0.24
Gastrointestinal cancer	1.325 (0.901–1.882)	0.15
Extracranial spread†	1.207 (0.962–1.509)	0.10
Control of primary cancer	0.919 (0.738–1.149)	0.46
Number of metastatic body sites	0.985 (0.908–1.065)	0.72
Gross total resection	0.949 (0.750–1.208)	0.67
Whole brain radiation†	0.819 (0.549–1.098)	0.09
Stereotactic radiosurgery	0.848 (0.669–1.068)	0.16
Perioperative variables associated with poorer survival		
New neurological deficit‡	5.1442 (1.956–1.209)	0.002
Not discharged to home‡	1.543 (1.151–2.049)	0.004
No postoperative brain radiation‡	2.058 (1.582–2.653)	0.001

These factors were independent of perioperative variables found to be associated with survival (new neurological deficit, postoperative brain radiation, and discharge to home).
CI, confidence interval; NSCLC, non-small cell lung cancer.
*In a separate multivariate model, tumor size was dichotomized into the multivariate analysis to find the greatest statistical association with survival.
†Associated in univariate analysis, but not in multivariate analysis.
‡Perioperative factors that were controlled for in the multivariate model.

gender remained significantly associated with survival (hazard ratio, 1.546; 95% CI 1.202–1.995; P = 0.0007).

Survival Based on RPA Class 2 Grade

Based on the multivariate analyses, the preoperative factors that were independently associated with poorer survival were male gender, preoperative motor deficit, preoperative cognitive deficit, nonsolitary metastasis, and tumor size >2 cm. One point was assigned for each of these factors. In this scoring system, patients with a prognostic grade A had 0–1 points, grade B had 2 points, and grade C had 3–5 points (Table 3). Kaplan-Meier plots were formed for each of the prognostic grades. Among these RPA class 2 patients, 97 were grade A, 137 were grade B, and 155 were grade C (Table 4). Thirty-two patients were excluded because they did not have sufficient preoperative information to assign a grade. The median survival for patients with a grade A classification was 17 months, grade B was 10.3 months, and grade C was 7.3 months. RPA class 2 patients with a preoperative grade A had a significantly longer survival than patients with a grade B (P = 0.01) and C (P < 0.0001). Likewise, patients with a preoperative grade B had a significantly longer survival than patients with a grade C (P = 0.009) (Figure 2B).

To make sure important perioperative factors were not significantly different among the prognostic grades, separate analyses were carried out. In multivariate analyses, the perioperative factors that were significantly associated with survival were new neurological deficit, discharge to rehabilitation, and postoperative brain radiation. With regard to new neurological deficits, grade A patients had no significant differences compared with grade B (P = 0.21) and C patients (P = 0.20). Likewise, there were no significant differences in incidence of new neurological deficits between grades B and C patients (P = 0.99). With regard to discharge to rehabilitation, grade A patients had no significant differences compared with grade B (P = 0.56) and C patients (P = 0.30). Likewise, there were no significant differences in discharges to rehabilitation between grade B and C patients (P = 0.67).

Table 3. Surgical Prognostic Scoring System for Recursive Partitioning Analysis Class 2 Patients with Intracranial Metastases

Prognostic Metastatic Scoring System

Variables	Yes	No
Male	1	0
Motor deficit	1	0
Cognitive deficit	1	0
Nonsolitary metastasis	1	0
Tumor size >2 cm	1	0

In this scoring system, patients with a prognostic grade A had 0–1 points, grade B had 2 points, and grade C had 3–5 points.

Table 4. Survival Outcomes for the Different Prognostic Grades

Surgical Outcomes by Different Prognostic Grades

	Grade A (n = 97)	Grade B (n = 137)	Grade C (n = 155)
Median survival (months)	17.0	10.3	7.3
6-month survival rate	74.7%	64.6%	55.1%
12-month survival rate	55.9%	45.6%	30.7%
18-month survival rate	48.9%	33.2%	18.6%
24-month survival rate	41.5%	27.0%	15.8%

All classes had statistically different survival rates ($P < 0.05$).

Finally, with regard to postoperative brain radiation, grade A patients had no significant differences compared with grade B ($P = 0.26$) and C patients ($P = 0.99$). Likewise, there were no significant differences in radiation between grade B and C patients ($P = 0.30$). Furthermore, when just evaluating patients who underwent postoperative radiation, grade A patients had statistically longer survival times than grade B (18.6 vs. 14.2 months; $P = 0.03$) and grade C (18.6 vs. 7.2 months; $P < 0.0001$) patients. Likewise, grade B patients had longer survival than grade C patients (14.2 vs. 7.2 months; $P = 0.001$).

DISCUSSION

In this series of 421 RPA class 2 patients who underwent surgery for single or multiple intracranial metastases, 324 (77%) patients died at last follow-up and the median survival was 9.6 months. The 6-, 12-, and 18-month survival rates were 62.4%, 42.4%, and 31.2%, respectively. After controlling for perioperative factors found to be associated with survival (new neurological deficit, not discharged to home, no radiation therapy), the preoperative factors independently associated with decreased survival were male gender, preoperative motor deficit, preoperative cognitive deficit, nonsolitary metastases, and tumor size >2 cm. Patients with an increased number of these preoperative variables had statistically significant poorer survival, regardless of perioperative treatment.

RPA-Based Studies

Patients with metastatic disease have disparate survival times (2-6, 11, 13-15). In general, as for other types of malignancies, surgery, and more aggressive therapies are usually offered to patients with better anticipated survival, but are withheld from patients with poor prognoses (10, 12, 16, 24). The RPA classification system was designed to identify patients with metastatic disease who had better and worse prognoses (15, 25, 26, 30, 33). This three-tiered system is based on age, KPS, primary tumor control, and extracranial disease (15, 25, 26, 30, 33). RPA class 1 patients have the best prognoses because they are of relatively young (aged <65 years), have good performance status (KPS ≥70), primary tumor control, and no extracranial disease (15). RPA class 3 patients have the worst prognoses because they have poor performance status (KPS <70) (15). RPA class 2 patients, however, represent a heterogeneous group with disparate preoperative characteristics and therefore survival times (15, 25, 26, 30, 33). This group of patients is characterized by having good performance status, but some combination of older age, lack of primary tumor control, and/or presence of extracranial disease (15). As a result of this disparity, there have been other attempts to establish more in-depth grading systems including the graded prognostic assessment (GPA), score index for radiosurgery, and basic score for brain metastases (20, 31, 32, 36). These grading systems, however, are more cumbersome, less accurate and reliable in predicting survival, and less widely used compared with the RPA classification system (20, 31, 32, 36). Nevertheless, the ability to offer more or less aggressive therapies based on understanding prognoses for RPA class 2 patients remains limited.

Prior large surgical studies on patients with intracranial metastatic disease are few and limited (Table 5). Rades et al. (27) studied 195 patients who underwent surgery and WBRT, with or without SRS, for solitary brain metastasis. They found that younger age, improved KPS, RPA class 1, and absence of extracranial disease were independently associated with survival. Likewise, Niwinska et al. (23) evaluated 57 of 100 patients who underwent surgery for a solitary breast metastasis, and found that RPA class 1, systemic therapy, and surgery were associated with survival. Karlovits et al. (19) studied patients with four or less metastases, and found that solitary metastasis and lack of extracranial disease were associated with survival in 52 patients undergoing surgery for intracranial metastases. Tendulkar et al. (33) studied 271 patients who underwent solitary metastatic tumor resection, and found that RPA class and SRS were associated with improved survival. These surgical studies and others are limited by including all RPA classes (19, 23, 24, 27, 29, 33, 34), nonsurgical patients (23), only solitary metastases (23, 27, 29, 33), and limited histologies (23). This makes it difficult to discern prognoses for RPA class 2 patients, which is arguably the most controversial treatment group and represent up to 80% of patients with metastatic disease (15, 25, 26, 30, 33). In addition, it remains difficult to evaluate which RPA class 2 patients most benefit from surgical resection.

Preoperative Factors Independently Associated with Survival

Men had poorer survival than women in this study. This has been seen in previous nonsurgical studies (21, 35, 39). Videtic et al. (35) found this survival disparity between men and women who develop NSCLC brain metastases and underwent radiation therapy. The median survival for male patients was 5.5 months compared with 6.3 months for female patients. This improved survival for female patients has been attributed to gender differences in baseline health statuses, hormonal levels, and propensity for different tumor types (21, 35, 39).

The presence of motor and/or cognitive deficits was also independently associated with poorer survival for RPA class 2 patients. The presence of motor and cognitive deficits made it 1.6- and 1.8-fold

Table 5. Summary of Previous Surgical Studies with >50 Patients on Prognosticating Outcomes for Patients with Intracranial Metastases

Studies	Year	Number of Surgical Patients	Patients with Multiple Metastases	All Types of Metastases	RPA Classes Included
Present study	2012	421	Yes	Yes	2
Rades et al. (27)	2012	195	No	Yes	1–3
Niwinska et al. (23)	2011	57	No	No	1–3
Karlovits et al. (19)	2009	52	Yes	Yes	1–3
Tendulkar et al. (33)	2006	271	No	Yes	1–3
Paek et al. (24)	2005	280	Yes	Yes	1–3
Vecil et al. (34)	2005	61	Yes	Yes	1–3
Regine et al. (29)	2004	95	No	Yes	1–2

RPA, recursive partitioning analysis.

more likely that a patient would have poorer survival, respectively. The fact that this study contained only patients with high performance statuses (KPS ≥70) indicates that even minor motor and/or cognitive deficits can be associated with poorer survival. Tumors causing these early deficits can be more difficult to treat surgically as a result of location and/or swelling, and potentially have a propensity for poorer outcomes.

Patients who presented with multiple metastases and who had larger tumors also had poorer survival in this study. This poorer prognosis for patients with multiple intracranial metastases has also been seen in studies that included all RPA classes, where patients with solitary metastasis had the best prognoses (8, 18, 28, 37, 38, 40). Patients, however, rarely only have one metastasis, especially with advances in neuroimaging modalities (8, 18, 28, 37, 38, 40). Similarly, tumor size was also independently associated with poorer survival in this study, where the most significant cutoff was 2 cm. Larger tumors may indicate more tumor burden, which may make these tumors less responsive to surgical and adjuvant therapies. This same size cutoff is used for radiation algorithms, where tumors larger than 2 cm typically do not respond to radiation therapy (7, 17). Surgery, as with radiation therapy, is most efficacious for smaller tumors.

Preoperative Classification Scale

The most commonly used classification system for patients with metastatic disease is the RPA classification system (15). Gaspar et al. (15) used patient populations from the Radiation Treatment and Oncology Group from three consecutive studies from 1979 to 1993. Based on these 1200 patients who underwent radiation therapy, they devised a three-tiered system based on age, performance status, primary tumor control, and extracranial disease. This has been validated by several other SRS, WBRT, and surgical studies (15, 25, 26, 30, 33). The GPA classification system was designed to address the shortcomings of the RPA classification system (31, 32). This classification system used 1960 patients from five clinical studies, and divided age, KPS, number of intracranial metastases, and presence of extracranial disease into three different subgroups (31, 32). This classification system, however, was only useful for NSCLC and small cell lung cancer, and most patients were classified into the poor prognostic group (31, 32). Likewise, the score index for radiosurgery was used to prognosticate outcomes for patients who underwent SRS (36). Similar to the GPA system, each category is subdivided into three different categories (36). This scale, however, is only applicable to patients undergoing SRS and therefore typically only applies to tumors that are smaller, radiosensitive, and less numerous (36).

The inability of RPA and non-RPA classification schemes to prognosticate survival for RPA class 2 patients who undergo surgery has made it difficult to anticipate survival outcomes and thus guide treatment regimens for this group of patients. Based on this premise, we devised a preoperative classification scale using factors independently associated with survival for patients who underwent surgery (Table 3). This classification system identifies three distinct populations with statistically different survival rates. Important, these classes are independent of perioperative factors found to be associated with survival, and can therefore be applied before any treatment is pursued. This would allow physicians and patients to prognosticate survival after surgery, which may play an important role in developing individualized surgical and medical approaches.

Strengths and Limitations

We believe this study provides several useful insights for patients with metastatic disease who undergo intracranial surgery or are considering intracranial surgery. First, studies dedicated to RPA class 2 patients are few and limited. The present study identifies male gender, motor deficit, cognitive deficit, nonsolitary metastasis, and tumor size >2 cm as independently associated with poorer survival. Second, studies applying preoperative risk factors in a manner that provides useful prognostic information have yet to be established for RPA class 2 patients. This study provides a potentially useful three-tier system that may prognosticate survival independent of perioperative factors before any treatment is pursued. Last, this study may provide useful information that may help guide treatment strategies aimed at optimizing interventions for RPA class 2 patients. These findings can help surgeons, oncologists, patients, and their families anticipate surgical outcomes, as well as help in the treatment plan decision making. For example, patients with favorable prognoses among RPA class 2 patients may act more similar to their RPA class 1 counterparts, and therefore treatment plans can be more similar to those used for RPA class 1 patients. Patients with poor prognoses among RPA class 2 patients, although they still do better than RPA class 3 patients historically, may not benefit from more aggressive and burdensome regimens usually reserved for patients with better prognoses.

This study, however, has some limitations. One limitation is that the findings of this study only apply to RPA class 2 patients undergoing surgery for intracranial metastases. All the patients in this study underwent intracranial surgery, and it is therefore not appropriate to apply these findings to RPA class 2 patients who did not undergo surgery. An additional limitation is the need for external validation of this prognostic classification scale in a prospectively followed cohort. This process is currently ongoing. In addition, this study also does not analyze the prognostic implication of molecular markers and genotypes, which may be associated with survival. Furthermore, a significant number of patients in this study did not undergo GTR, WBRT, and/or SRS. As a result, the relevance of this prognostic model may be altered in the context of receiving the most aggressive treatment regimens. Also, tumor histology was evaluated, but no specific histology was independently associated with survival. Ideal studies would be isolated to particular pathologies, which is not practical unless using a national database. In addition, this study is inherently limited by its retrospective design, and, therefore, it is not appropriate to infer direct causal relationships. However, we tried to create a uniform patient population by using strict inclusion criteria to provide more relevant information for RPA class 2 patients who underwent surgery of their intracranial metastases. We performed multivariate analyses and controlled for potential perioperative confounding variables. Given these statistical controls and a relatively precise outcome measure, we believe our findings offer useful insights into the management of RPA class 2 patients. However, prospective studies are needed to provide better data to guide clinical decision making.

CONCLUSION

This study evaluates the outcomes after surgery for RPA class 2 patients, and attempts to prognosticate survival after surgery. The present study found that male gender, motor deficit, cognitive deficit, tumor size, and number of metastases were independently associated with survival for patients in the RPA class 2. A classification system based on these factors was able to identify three distinct groups of patients with different survival rates. This classification system, based on preoperative variables, may provide patients and physicians with prognostic information that may guide medical and surgical therapy for RPA class 2 patients.

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