Evaluation of Prognostic Factors for Early Mortality After Stereotactic Radiosurgery for Brain Metastases: a Single Institutional Retrospective Review

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BACKGROUND: Stereotactic radiosurgery (SRS) is used commonly for patients with brain metastases (BM) to improve intracranial disease control. However, survival of these patients is often dictated by their systemic disease course. The value of SRS becomes less clear in patients with anticipated short survival.

OBJECTIVE: To evaluate prognostic factors, which may predict early death (within 90 d) after SRS.

METHODS: A total of 1427 patients with BM were treated with SRS at our institution (2000-2012). There were 1385 cases included in this study; 1057 patients underwent upfront SRS and 328 underwent salvage SRS. The primary endpoint of the study was all-cause mortality within 90 d after first SRS. Multivariate analyses were performed to develop prognostic indices.

RESULTS: Two hundred sixty-six patients (19%, 95% confidence interval 17%-21%) died within 90 d after SRS. Multivariate analysis of upfront SRS patients showed that Karnofsky Performance Status, primary tumor type, extracranial metastases, age at SRS, boost treatment, total tumor volume, prior surgery, and interval from primary to BM were independent prognostic factors for 90-d mortality. The first 4 factors were also independent predictors in patients treated with salvage SRS. Based on these factors, an index was defined for each group that categorized patients into 3 and 2 prognostic groups, respectively. Ninety-day mortality was 5% to 7% in the most favorable cohort and 36% to 39% in the least favorable.

CONCLUSION: Indices based on readily available patient, clinical, and treatment factors that are highly predictive of early death in patients treated with upfront or salvage SRS can be calculated and used to define well-separated prognostic groups.

KEYWORDS: Brain metastasis, Early mortality, Prognostic factors, Stereotactic radiosurgery

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Nearly one-third of all cancer patients will develop brain metastases (BM).[1,2] Prognosis of these patients is most often dictated by the course of their systemic disease, but a subset of patients may survive past 1 yr.[2-5] Due to the poor response to systemic agents, treatment of BM generally includes radiotherapy, surgery, or a combination of treatments.[5-8] Stereotactic radiosurgery (SRS) is a favorable treatment option in patients with a limited number of BM.[6-11] Compared to whole brain radiotherapy (WBRT), SRS offers more localized control avoiding significant acute and long-term toxicities.[6-8,10,11]

ABBREVIATIONS: BM, brain metastases; **GPA,** graded prognostic index; **KPS,** Karnofsky Performance Status; **NSCLC,** nonsmall cell lung cancer; **QOL,** quality of life; **RPA,** recursive partitioning analysis; **RTOG,** Radiation Therapy Oncology Group; **SRS,** stereotactic radiosurgery; **WBRT,** whole brain radiotherapy

Due to the heterogeneity of this patient population, multiple prognostic indices have been developed to guide physicians in their individualized treatments.[12] Initially, recursive partitioning analysis (RPA) was published stratifying BM patients into 3 outcomes groups.[3] In 2008, an updated prognostic index, the graded prognostic index (GPA), was developed and

later refined into diagnosis-specific indices.[4,12,13] Based on these indices, prognostic factors in patients with BM varied considerably by tumor type.[4,12] However, in patients with a low GPA of 0 to 1.0 expected survival was approximately 3 mo irrespective of diagnosis.[12] Of note, both RPA and GPA are based on older Radiation Therapy Oncology Group (RTOG) trials with WBRT as the primary radiation treatment.[2,4,12,13]

With the use of SRS alone, developing indices to help providers identify those who will benefit most from SRS is of importance.[6] We therefore evaluated which prognostic factors may predict early death (within 90 d) after SRS in patients with BM.

METHODS

Patient Selection

The Cleveland Clinic institutional review board approval was obtained for this retrospective cohort study. Consent was not obtained for this retrospective study given there was no interaction with individuals or identifiable private information utilized in this study. We evaluated all patients who underwent SRS for BM between the year 2000 and 2012. Patient data were obtained from patients' electronic medical record and from our institution's brain tumor database. Patients were included if they had BM and underwent SRS.

Treatment Details

For full details regarding our protocol for treatment of BM, see our prior publication.[14] In brief, both high-resolution MR images (Magnetization-Prepared Rapid Gradient-Echo 1-mm slices; preframe or postframe) and CT scanning of the brain were performed on all patients. If needed, MR images are supplemented by contrast-enhanced T1-weighted imaging (2-mm slices) for planning of targets. MRI-CT image matching is performed to improve accuracy and identify distortion of MRI sequences. Tumors were treated based on their size per RTOG 90-05 dosing protocol and all were treated with 50% to 90% isodose lines.[15]

Statistical Methods

The primary endpoint was all-cause 90-d mortality measured from the date of SRS. Categorical data were analyzed as frequency counts and percentages, whereas continuous data, such as tumor volume, were evaluated using medians and ranges. Neurological functional status was defined as normal, mild, or moderate/severe based on an adaption of the neurological function score defined by Shaw et al.[15] Moderate symptoms were combined into 1 group for our classification. For patients with at least 90 d of potential follow-up, 90-d mortality was dichotomized as survival <90 d vs > 90 d, and overall survival was summarized using the method of Kaplan and Meier. Univariate analyses of 90-d mortality between patient groups were performed using Fisher's exact test and χ^2 tests for unordered categorical factors. The Cochran-Armitage trend test was used for ordered categorical factors, and the Wilcoxon rank-sum test was used for continuous factors. Log-rank tests were used for comparisons of overall survival. For convenience, a recursive partitioning algorithm was used to categorize continuous factors.[16]

Multivariate analysis to identify independent prognostic factors for 90-d mortality was conducted using binary logistic regression and stepwise model selection with $P = .10$ and .05 as the criteria for variable entry and retention in the model. Separate analyses were performed for patients treated with upfront SRS and those treated with SRS as salvage therapy. With the exception of RPA and age at diagnosis of the primary and age at BM, all the factors in Table 1 were initially considered for inclusion in each model. RPA was not included because the vast majority of patients were class 2 (85% of upfront patients and 75% of patients treated with salvage SRS). Age at the primary diagnosis and the diagnosis at BM were not included because of their high correlation with age at SRS. For convenience, only the categorical versions of continuous factors were considered.

Once a final model was defined, a prognostic index was created by assigning weights to the levels of each factor that were approximately proportional to the corresponding regression coefficients and then summing the individual weights for each patient.[17-19] The weights were derived by dividing each regression coefficient by the smallest one present in the model, multiplying the result by 2 and then rounding to the nearest integer. In doing this, integer weights were obtained that were convenient to use and that reflected the differences in the magnitude of effect between factors seen in the final model. Using this index, prognostic groups were then formed using Cox's suggestion on combining groups.[20] All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Participants

A total of 1427 patients with BM were treated with SRS between 2000 and 2012 at our institution and were considered for initial analysis and examined for eligibility. Forty-two patients were excluded for the following reasons: glioblastoma multiforme pathology after failure of SRS and surgery (n = 1), age at diagnosis <18 (n = 4), missing or inconsistent data (n = 27), less than 90 d of potential follow-up (n = 10). A total of 1385 patients were therefore confirmed eligible and included in the study.

Descriptive Data

Overall 53% of patients were female. Median ages were 58 (range 20-92) at primary lesion diagnosis, 59 (range 20-92) at diagnosis of BM, and 60 (range 24-92) at SRS treatment. Most patients developed BM shortly after primary diagnosis (median 11 mo). The most common primary cancers were nonsmall cell lung cancer (NSCLC) (44%), breast cancer (16%), renal cancer (13%), and melanoma (9%). The majority of patients had good performance status (74% had Karnofsky Performance Status [KPS] > 80); still, a small but clinically significant number of patients had KPS < 60 (8%). The vast majority of patients fell into RPA class 2 (79%), and most were classified as having a relatively poor prognosis by GPA criteria (86% had scores <3). Furthermore, the majority of patients had at least mild neurological impairment (49% mild and 20% moderate or severe). Baseline patient characteristics and outcome categorized by treatment group are described in Table 1.

Outcome Data

Patients most commonly presented with 1 (45%) or 2 (24%) BM. The majority of lesions were <2 cm (55% of patients had

TABLE 1. Patient Characteristics and 90-d Mortality

Factor	Upfront SRS (n = 1057)			Salvage SRS (n = 328)		
	n (%) or median (range)	Median or n (%) deaths within 90 d of SRS[a]	*P* value[b]	n (%) or median (range)	Median or n (%) deaths within 90 d of SRS[a]	*P* value[b]
Gender						
Female	538 (51%)	84 (16%)		195 (59%)	32 (16%)	
Male	519 (49%)	117 (23%)	.005[c]	133 (41%)	33 (25%)	.073
Primary						
NSCLC	494 (47%)	111 (22%)		132 (40%)	31 (23%)	
Breast	158 (15%)	18 (11%)		67 (20%)	7 (10%)	
Renal	168 (16%)	31 (18%)		19 (6%)	3 (16%)	
Melanoma	97 (9%)	19 (20%)		27 (8%)	10 (37%)	
Other	138 (13%)	21 (15%)	.02	82 (25%)	13 (16%)	.03
Age at Dx of primary	59 (20-92)	58/60	.01	55 (21-79)	53/60	.004
Age at Dx of brain mets	60 (20-92)	60/62	.01	57 (24-80)	56/62	.007
Age at SRS	60 (24-92)	60/62	.01	58 (24-80)	57/63	.005
≤60	537 (51%)	92 (17%)		189 (58%)	26 (14%)	
>60	520 (49%)	109 (21%)	.12	139 (42%)	39 (28%)	.002
≤70	839 (79%)	137 (16%)		298 (91%)	58 (19%)	
>70	218 (21%)	64 (29%)	<.0001	30 (9%)	7 (23%)	.63
Interval from primary to brain mets (months)	11.0 (0-618.7)	12.0/8.0	.36	10.0(0-303.3)	11.0/8.0	.24
≤12	559 (53%)	122 (22%)		178 (54%)	39 (22%)	
>12	498 (47%)	79 (16%)	.01	150 (46%)	26 (17%)	.19
Prior surgery						
No	894 (85%)	186 (21%)		226 (69%)	44 (19%)	
Yes	158 (15%)	13 (8%)	<.0001	101 (31%)	21 (21%)	.77
KPS[d]						
90-100	524 (50%)	54 (10%)		124 (38%)	7 (6%)	
80	301 (28%)	71 (24%)		107 (33%)	24 (22%)	
70	161 (15%)	48 (30%)		60 (18%)	16 (27%)	
≤60	71 (7%)	28 (39%)	<.0001	36 (12%)	17 (47%)	<.0001
RPA						
Class 1	130 (12%)	7 (5%)		46 (14%)	1 (2%)	
Class 2	854 (81%)	166 (19%)		245 (75%)	46 (19%)	
Class 3	71 (7%)	28 (39%)	<.0001	36 (11%)	17 (47%)	<.0001
GPA						
0-1	205 (19%)	69 (34%)		104 (32%)	36 (35%)	
1.5-2.5	697 (66%)	119 (17%)		182 (56%)	26 (14%)	
3	112 (11%)	11 (10%)		26 (8%)	1 (4%)	
3.5-4	42 (4%)	2 (5%)	<.0001	14 (4%)	-0-	<.0001
Neurological function status						
Normal	338 (32%)	49 (14%)		93 (28%)	8 (9%)	
Mild impairment	526 (50%)	91 (17%)		157 (48%)	29 (18%)	
Moderate/severe[e]	192 (18%)	61 (32%)	<.0001	77 (24%)	27 (35%)	<.0001
Extracranial mets at SRS						
No	245 (23%)	24 (10%)		75 (23%)	7 (9%)	
Yes	812 (77%)	177 (22%)	<.0001	253 (77%)	58 (23%)	.008
Intracranial disease volume	2.5 (0.03-83.0)	2.4/2.9	.25	2.6 (0.03-49.4)	2.5/3.0	.21
<1.5 cc	394 (37%)	64 (16%)		106 (33%)	17 (17%)	
≥1.5 cc	662 (63%)	137 (21%)	.09	220 (67%)	48 (22%)	.24
Boost						
No	782 (74%)	136 (17%)		–		
Yes	275 (26%)	65 (24%)	.03	–		

TABLE 1. *Continued*

Factor	Upfront SRS (n = 1057)			Salvage SRS (n = 328)		
	n (%) or median (range)	Median or n (%) deaths within 90 d of SRS[a]	*P* value[b]	n (%) or median (range)	Median or n (%) deaths within 90 d of SRS[a]	*P* value[b]
Mean isodose line	54 (50-95)	53/54	.04	54 (50-87)	54/55	.56
<60%	836 (82%)	149 (18%)		251 (78%)	49 (20%)	
≥60%	185 (18%)	44 (24%)	.08	70 (22%)	15 (21%)	.74
Location of metastasis						
Infratentorial	137 (13%)	26 (19%)		35 (11%)	4 (11%)	
Supratentorial	707 (67%)	125 (18%)		160 (49%)	30 (19%)	
Both	213 (20%)	50 (23%)	.08[f]	132 (40%)	31 (23%)	.20
Brainstem involvement						
No	1009 (95%)	188 (19%)		299 (91%)	57 (19%)	
Yes	48 (5%)	13 (27%)	.18	28 (9%)	8 (29%)	.22
No. of targets	1 (1-12)	1/2	.02	2 (1-17)	2/3	.05
1	526 (50%)	82 (16%)		88 (27%)	15 (17%)	
2	240 (23%)	48 (20%)		95 (29%)	15 (16%)	
>2	290 (27%)	71 (24%)	.002	145 (44%)	35 (24%)	.21
No. of lesions >2 cm[g]						
0	587 (56%)	109 (19%)		177 (54%)	30 (17%)	
1	411 (39%)	73 (18%)		124 (38%)	26 (21%)	
2-3	59 (6%)	19 (32%)	.18	27 (8%)	9 (33%)	.06

NSCLC, nonsmall cell lung cancer.
[a]For continuous factors, the median for patients surviving beyond 90 d is given first followed by the median for patients who died within 90 d.
[b]Wilcoxon rank-sum test for continuous factors; Fisher's exact test, χ^2 test, or Cochran-Armitage trend test for categorical factors.
[c]Excluding breast cancer $P = .05$ with upfront SRS; $P = .17$ with salvage SRS.
[d]Upfront SRS—59 patients were KPS 100, 57 were KPS 60, 12 were KPS 50, and 2 were KPS 40; salvage SRS—7 patients were KPS 100, 26 were KPS 60, 9 were KPS 50, and 1 was KPS 40.
[e]Upfront SRS—21 patients had severe impairment; salvage SRS—14 patients had severe impairment.
[f]Infra- or supratentorial vs both.
[g]Upfront SRS—6 patients had 3 lesions >2 cm; salvage SRS—4 patients had 3 lesions >2.

no lesions over 2 cm) and were supratentorial in location (63%). The brainstem was involved in only 5% of cases. Overall median volume of disease for both resected and intact lesions was 2.5 cc (range 0.03-83.0 cc). Seventy-seven per cent of patients had extracranial metastasis at the time of SRS, and 19% of patients underwent prior surgical resections.

Main Results

Ninety-day mortality was 19% (95% confidence interval 17%-21%). Univariate and multivariate analysis were performed separately for upfront and salvage treatment subgroups. Overall mortality at 60 mo was 87% (n = 1216), with estimated median survival of 8.7 mo (95% confidence interval 8.1-9.4) and estimated 6- and 12-mo overall survivals of 62% ± 1% and 40% ± 1%, respectively (see Figure 1).

Upfront SRS

In univariate analysis for upfront treatments, a number of factors appeared to impact 90-d mortality (as shown in Table 1). Multivariate modeling was performed to determine which factors contained independent prognostic information. As described in

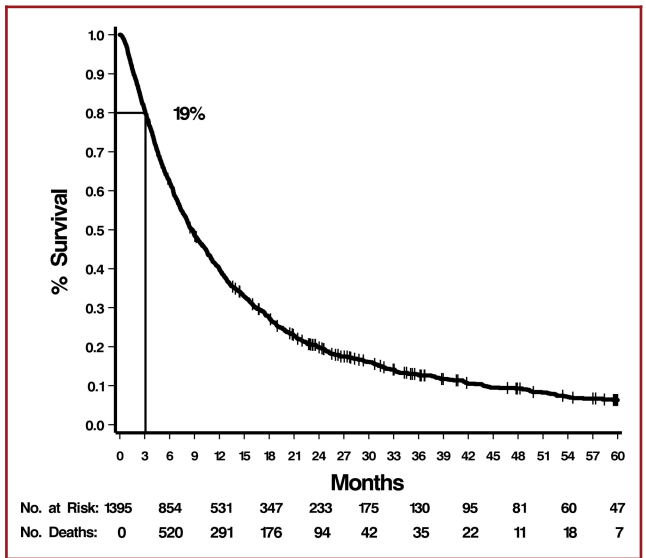

FIGURE 1. *Overall Survival. A Kaplan-Meier surival curve for the overall cohort including numbers at risk and deaths over the follow-up period.*

TABLE 2. Multivariate Analysis—Upfront SRS

Factor	Regression Coefficient ± SE[a]	Odds ratio (95% CI)[a]	*P* value[b]	"Points"[c]
Intercept	1.17 ± 0.30	–	.0001	–
Primary tumor				
NSCLC (male)	Reference	–	–	0
NSCLC (female), melanoma	–0.42 ± 0.20	0.65 (0.44-0.97)	.04	2
Renal cell				
Breast, other	–0.84 ± 0.26	0.43 (0.26-0.71)	.001	4
KPS				
≤70	Reference	–	–	0
80	–0.42 ± 0.21	0.66 (0.43-0.99)	.05	2
90-100	–1.40 ± 0.22	0.25 (0.16-0.38)	<.0001	7
Extracranial mets				
Yes	Reference	–	–	0
No	–1.22 ± 0.25	0.30 (0.18-0.48)	<.0001	6
Prior surgery				
No	Reference	–	–	0
Yes	–1.11 ± 0.32	0.33 (0.18-0.61)	.0005	6
Age at SRS				
≥70	Reference	–	–	0
<70	–0.60 ± 0.20	0.55 (0.37-0.82)	.003	3
Boost				
Yes	Reference	–	–	0
No	–0.54 ± 0.19	0.58 (0.40-0.85)	.004	3
Total tumor volume				
≥15 cc	Reference	–	–	0
<15 cc	–0.45 ± 0.18	0.64 (0.45-0.92)	.02	2
Interval from primary to brain mets				
>12 mo	Reference	–	–	0
≤ 12 mo	–0.40 ± 0.19	0.67 (0.46-0.96)	.03	2

SE, standard error; CI, confidence interval; NSCLC, nonsmall cell lung cancer.
[a]Models the odds of death within 90 d; odd ratios are $\exp^{\text{regression coefficient}}$; an odds ratio being <1 indicates the category has a better prognosis than the reference.
[b]Wald test.
[c]In order to create simple integer weights that preserve (approximately) the observed differences in the magnitude of effect between factors "points" for each factor were determined by dividing the regression coefficient associated with the factor by the value of the smallest one listed (–0.40), multiplying by 2, and rounding to the nearest integer.

the methods, stepwise model selection was utilized to identify predictors of 90-d mortality among upfront SRS group. For KPS and primary histology (0,1), indicators were used for the different levels of each factor; however, for nonsmall cell lung cancer, 2 indicators were used, 1 for males and 1 for females, because preliminary analyses indicated that outcome differed by sex. In modeling the data, there were no significant differences between some of the KPS scores and some histologies and they were therefore combined in the final model, which is summarized in Table 2. As can be seen, KPS, primary tumor, presence of extracranial metastases, age at SRS, boost treatment, total tumor volume, prior surgery, and interval from primary to BM were independent prognostic factors for 90-d mortality after upfront SRS.

Using these results presented in Table 2, a simple scoring system was used to build a prognostic index. That is, by assigning "points" (weights) to the levels of each factor that are roughly proportional to the associated regression coefficients in the final model, an index was defined that simply sums the number points present. The index ranges from 0 (worst prognosis) to 33 (best prognosis) and was used to define 3 prognostic groups (see Table 3). Patients with a favorable profile were those whose index was >17. This group comprised 28% of patients and had an observed 90-d mortality rate of 5% with a 1-yr survival rate of 60%. Patients whose index was <11 were considered unfavorable. Twenty-eight per cent of patients were so categorized and the observed 90-d mortality was 39% with a 1-yr survival rate of 23%. Patients in the intermediate groups had scores of 12 to 17, comprised 44% patients, and had observed 90-d mortality of 15%. The prognostic index was also associated with overall survival ($P <$ .0001, data not shown).

Salvage SRS

When we evaluated those patients who had SRS as a salvage treatment (n = 328), primary tumor type, KPS, extracranial

TABLE 3. Prognostic Index for 90-d Mortality in Upfront SRS

Group	No. of points	n	90-d mortality	1-yr Surv ± SE.	2-yr Surv ± SE	*P* value[a]
Unfavorable	≤11	290 (28%)	112 (39%)	23% ± 2%	9% ± 2%	
Intermediate	12-17	464 (44%)	70 (15%)	38% ± 2%	17% ± 2%	
Favorable	>17	295 (28%)	16 (5%)	60% ± 3%	37% ± 3%	<.0001

SE, standard error.
[a]Cochran-Armitage trend test for 90-d mortality, log-rank trend test for survival; both were significant at $P < .0001$.

TABLE 4. Multivariate Analysis—Salvage SRS

Multivariate analysis and weights ("points")

Factor	Regression Coefficient ± SE[a]	Odds ratio (95% CI)[a]	*P* value[b]	"Points"[c]
Intercept	−0.0142 ± 0.27	–	.96	–
Primary tumor				
NSCLC, melanoma	Reference	–	–	0
Breast, renal cell, other	−0.92 ± 0.32	0.40 (0.21-0.74)	.004	2
KPS				
≤80	Reference	–	–	0
>80	−1.54 ± 0.43	0.21 (0.09-0.50)	.0004	4
Extracranial mets				
Yes	Reference	–	–	0
No	−1.20 ± 0.45	0.30 (0.12-0.72)	.007	3
Age at SRS				
>60	Reference	–	–	0
≤60	−0.80 ± 0.31	0.45 (0.24-0.83)	.01	2

SE, standard error; CI, confidence interval; NSCLC, nonsmall cell lung cancer.
[a]Models the odds of death within 90 d; odd ratios are $\exp^{\text{regression coefficient}}$; an odds ratio being <1 indicates the category has a better prognosis than the reference.
[b]Wald test.
[c]In order to create simple integer weights that preserve (approximately) the observed differences in the magnitude of effect between factors "points" for each factor were determined by dividing the regression coefficient associated with the factor by the value of the smallest one listed (−0.80), multiplying by 2, and rounding to the nearest integer.

TABLE 5. Prognostic Index for 90-d Mortality in Salvage SRS

Group	No. of points	n	90-d mortality	1-yr Surv ± SE	2-yr Surv ± SE	*P* value[a]
Unfavorable	≤3	140 (43%)	50 (36%)	22% ± 4%	9% ± 3%	
Favorable	>3	186 (57%)	13 (7%)	54% ± 4%	24% ± 3%	<.0001

[a]Fisher's exact test for 90-d mortality, log-rank test for survival; both were significant at $P < .0001$.

metastasis at diagnosis, and age at SRS were again found to be significant on multivariate analysis. Using the same approach as was used for upfront SRS, a prognostic index for 90-d mortality was defined based on these factors and summarized using a simple scoring system. The salvage SRS index ranged from 0 (worst prognosis) to 11 (best prognosis) and was used to define 2 prognostic groups (see Tables 4 and 5).

DISCUSSION

Key Results

SRS has more recently emerged as the preferred treatment modality in patients with limited BM and in those patients expected to have longer overall survival.[2,6] In patients with very short survival due to extensive intracranial or systemic

burden of disease, more palliative treatments such as WBRT or chemotherapy may be more appropriate than SRS.

Early prognostic indices, such as the RPA and GPA, were developed to predict survival in patients with BM primarily undergoing WBRT.[2,4,12,13] Prognostic models evaluating SRS as the primary treatment regimen have also been developed.[21,22] The prognostic models, however, focus on the longevity and do not necessarily predict for early morality. We therefore aimed to specifically identify and evaluate prognostic factors associated with death within 90 d following SRS.

In our cohort, 90-d mortality was 19%. Furthermore, median overall survival following SRS for BM was 8.7 mo, which is similar to the median survival reported in other studies following SRS.[21-23] Although a large number of prognostic factors were individually associated with early mortality, primary tumor type, KPS, extracranial metastasis, prior surgery, age at SRS, boost treatment, total tumor volume, and interval from primary diagnosis to BM remained independently prognostic for 90-d mortality in the upfront SRS cohort. In those receiving SRS as salvage treatment, only primary tumor type, KPS, extracranial metastasis, and age at SRS remained independently significant for 90-d mortality.

Based on these results, 2 prognostic indices for 90-d mortality were developed by stratifying patients into 3 groups and 2 groups based on a weighted scoring system. Ninety-day mortality in the unfavorable groups were 39% and 36% compared to 5% and 7% in the favorable groups for upfront and salvage SRS cohorts, respectively.

Gorovets et al[2] also studied patients with BM with $\geq$1 yr WBRT-free survival compared to those who died or required salvage WBRT within 3 mo of SRS. Median overall survival in their patient population was 11 mo. Their longer median overall survival compared to our study is likely attributable to patient selection. We on average included a higher portion of patients who had undergone prior WBRT, had worse KPS scores, and were more likely to have extracranial metastasis. Eighteen per cent of their patients died or required salvage WBRT within 3 mo of SRS. Increased number of BM and extracranial metastatic disease were more common amongst this subset of patients.

Kondziolka et al[24] also compared amongst 44 patients with BM prolonged survival ($\geq$4 yr) to those with limited survival (<3 mo) following SRS.[24] They found that long-term survival was associated with higher KPS, fewer BMs, and less extracranial disease. Our results are similar to these results. We also found those without prior surgeries were more likely to have earlier death.

Increased tumor volume has been shown to be associated with mortality in recent studies.[25-27] Kondziolka et al[25] found larger tumor volume per patient and increased volume of the largest tumor was associated with worse patient survival in 350 patients with breast cancer who underwent SRS for BM. Furthermore, Shultz et al[27] found that tumor volume over multiple courses of SRS was predictive of overall survival in BM patients undergoing 2 or more courses of SRS. They did not find that cumulative number of BMs was associated with survival. We similarly found that intracranial tumor volume was associated with high risk of early mortality following upfront SRS treatment.

Aggressive treatment with expensive interventions, such as SRS, in patients with high early mortality may not be appropriate. In this subgroup of patients, supportive care or less expensive treatment options may be more appropriate. As above, our model predicts that the least favorable group has a 35% to 40% chance of death within 90 d of SRS regardless of whether treatment is upfront or salvage. Kimmell et al[28] recently performed a comparative effectiveness analysis for single BM treatments including surgery, WBRT, and SRS, alone or in combination. They concluded that SRS was the most efficacious with the longest median survival and lowest recurrence rate but also had the greatest median cost. Therefore, SRS may not have the greatest cost-effectiveness for those with extremely poor prognosis.

However, Chen et al[29] recently evaluated patients aged $\geq$70 and $\geq$80 who underwent treatment of BM with upfront WBRT vs SRS. They found that those patients treated with upfront WBRT had significantly increased acute toxicity, which suggests that they were offering more toxic and time intensive treatment regimens to the patients with the worst prognosis.[29] Recently, no difference was found in overall survival and quality of life (QOL) when comparing WBRT with supportive care in the QUARTZ trial. Additional prospective studies evaluating the various treatment regimens in those with poor prognosis and expected early death are needed.[29-31]

In general, patients with poor performance status, poor GPA, and/or uncontrolled extracranial disease are not considered for SRS. Excluding those patients, still many more undergoing SRS will have early demise.[32] The proposed model helps identify patients at high risk for early mortality following SRS and therefore may help select those patients where the value of SRS for BMs is less clear.

Limitations and Generalizability

Our results are limited by the retrospective and nonrandomized nature of this study design. Based on this, there are inevitable confounding factors in terms of patient selection for radiosurgery, limited follow-up in some patients because of local or out of state follow-up, and insufficient data available in patient charts earlier in the series. Furthermore, our patients also had a high percentage of extracranial metastasis at the time of SRS and almost half had prior WBRT. These results may only be generalizable to similar patient populations. We also had obvious selection bias, which is inherent in retrospective studies. For instance, patients with prior surgery had better outcomes since we normally select patients with better KPS and limited extent of disease for surgery. On the other hand, patient with boost SRS had worse outcome compared with upfront SRS. This is probably a result of considering a boost SRS for patients with extensive intracranial disease

that need WBRT or for patients with larger lesions. A patient with good KPS and limited intracranial disease directly undergoes SRS.

One may argue there is a QOL benefit of preforming SRS over WBRT in a patient with short survival. We did not evaluate QOL outcomes in this study. However, if the prognosis is extremely dismal, performing either procedure for a QOL benefit alone may be questionable and actually diminish their QOL due to the side effects of such treatment. Further research is needed to examine the QOL in patients with BM who undergo the various radiation treatments as well as conservative management alone, especially when prognosis is poor. Additionally, with the advent of newer systemic treatments, such as programmed cell death protein 1 inhibitors, the outcomes for patients with systemic disease may be improved, which may enhance QOL as well and affect overall short-term prognosis. Incorporating newer systemic treatments into future research will thus be important.

Interpretation

Our results identified primary histology, KPS, presence of extracranial metastasis, and age at SRS as independent factors associated with mortality at 90 d after SRS in both the upfront and salvage setting. In patients treated with upfront SRS, prior surgery, boost treatment, total tumor volume, and the interval from primary diagnosis to BM were additional independent predictors. The resulting prognostic models may aid clinicians in the treatment decision making in patients with BM provide a valuable tool for appropriate clinical resource utilization, and may aid in clinical trial development. These models need to be validated prospectively.

CONCLUSION

An index based on patients' KPS, presence of extracranial metastasis, primary tumor type, age at SRS, boost treatment, total tumor volume, interval from primary to BM, and prior surgery was highly prognostic for 90-d mortality and can be used to define 3 distinct risk groups for patients undergoing upfront SRS. A similarly derived index based on just the first 4 of these factors can be used to define 2 prognostic groups in patients treated with salvage SRS. The proposed indices may provide a valuable tool for appropriate clinical resource utilization but need to be validated prospectively.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Mehta MP, Tsao MN, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys*. 2005;63(1):37-46.
2. Gorovets D, Rava P, Ebner DK, et al. Predictors for long-term survival free from whole brain radiation therapy in patients treated with radiosurgery for limited brain metastases. *Front Oncol*. 2015;5:110.
3. 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*. 1997;37(4):745-751.
4. 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*. 2010;77(3):655-661.
5. Brennan C, Yang TJ, Hilden P, et al. A phase 2 trial of stereotactic radiosurgery boost after surgical resection for brain metastases. *Int J Radiat Oncol Biol Phys*. 2014;88(1):130-136.
6. Yang TJ, Oh JH, Folkert MR, et al. Outcomes and prognostic factors in women with 1 to 3 breast cancer brain metastases treated with definitive stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys*. 2014;90(3):518-525.
7. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA*. 1998;280(17):1485-1489.
8. Patchell RA. The management of brain metastases. *Cancer Treat Rev*. 2003;29(6):533-540.
9. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*. 2006;295(21):2483-2491.
10. Sneed PK, Suh JH, Goetsch SJ, et al. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol Phys*. 2002;53(3):519-526.
11. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952–26001 study. *J Clin Oncol*. 2011;29(2):134-141.
12. 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*. 2012;30(4):419-425.
13. 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*. 2008;70(2):510-514.
14. Mohammadi AM, Recinos PF, Barnett GH, et al. Role of Gamma Knife surgery in patients with 5 or more brain metastases. *J Neurosurg*. 2012;117(suppl):5-12.
15. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys*. 2000;47(2):291-298.
16. Zhang HaSB. *Recursive Partioning in the Health Sciences*. Vol 1. New York: Springer; 1999.
17. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89(6):2079-2088.
18. Bahlo J, Kutsch N, Bauer K, et al.. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol*. 2016;17(6):779-790.
19. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. *Circulation*. 2002;105(3):310-315.
20. Cox DR. Note on Grouping. *J Am Stat Assoc* 1957;52(280):543-547.
21. 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*. 2012;83(5):1399-1405.
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*. 2000;46(5):1155-1161.
23. Gonda DD, Kim TE, Goetsch SJ, et al. Prognostic factors for stereotactic radiosurgery-treated patients with cerebral metastasis: implications on randomised control trial design and inter-institutional collaboration. *Eur J Cancer*. 2014;50(6):1148-1158.
24. Kondziolka D. The biological advantage of single-session radiosurgery. *J Neurosurg*. 2013;119(5):1129-1130; discussion 1130.
25. Kondziolka D, Kano H, Harrison GL, et al. Stereotactic radiosurgery as primary and salvage treatment for brain metastases from breast cancer. Clinical article. *J Neurosurg*. 2011;114(3):792-800.

26. Kaul D, Angelidis A, Budach V, Ghadjar P, Kufeld M, Badakhshi H. Prognostic indices in stereotactic radiotherapy of brain metastases of non-small cell lung cancer. *Radiat Oncol*. 2015;10:244.
27. Shultz DB, Modlin LA, Jayachandran P, et al. Repeat courses of stereotactic radiosurgery (SRS), deferring whole-brain irradiation, for new brain metastases after initial SRS. *Int J Radiat Oncol Biol Phys*. 2015;92(5):993-999.
28. Kimmell KT, LaSota E, Weil RJ, Marko NF. Comparative effectiveness analysis of treatment options for single brain metastasis. *World Neurosurg*. 2015;84(5):1316-1332.
29. Chen L, Shen C, Redmond K, et al. Use of stereotactic radiosurgery in elderly and very elderly patients with brain metastases to limit toxicity associated with whole brain radiation therapy. *Int J Radiat Oncol Biol Phys*. 2017;98(4):939-947.
30. Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD. Radiosurgery with or without whole-brain radiotherapy for brain metastases: the patients' perspective regarding complications. *Am J Clin Oncol*. 2005;28(2):173-179.
31. Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet*. 2016;388(10055):2004-2014.
32. Ampil FL, Caldito G, Mills G, Marion J, Balandin A, Ponugupati J. Short survival after palliative radiotherapy for brain metastases in lung cancer: does the end justify the means? *Am J Hosp Palliat Care*. 2013;30(4):331-333.

COMMENTS

The authors should be commended for their work on evaluating prognostic factors for early mortality after stereotactic radiosurgery for brain metastases. This issue is quite significant for practitioners of radiosurgery because of its increasing use and how health care reimbursement is moving towards performance-based models. Patients who have a 2-month survival after radiosurgery probably have a lesser benefit than a patient who has a 2-year survival, particularly if the patient with the 2-year survival has been able to avoid whole brain radiotherapy in that interval. It should be noted, however, that more data is necessary and that the current study is limited by the fact that it identifies risk factors for early death after radiosurgery, not predictive factors for benefiting from radiosurgery. A patient who has a symptomatic brain metastasis that is treated with radiosurgery alone may still avoid the toxicities of whole brain radiotherapy, while also having symptomatic improvement from the brain metastasis. However, these data can be used to help guide treatment decisions based on prognosticating survival. Future models will hopefully integrate quality of life, cost, and need for salvage as important variables to take into account.

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With the introduction of targeted agents and immunotherapy there has been an improvement in local control of primary disease with an increase in brain metastasis, some of which comes from MRI screening. The authors have developed a grading system to help predict early death after SRS. This paper evaluated patients who had SRS alone as well as those who had received whole brain radiation. The data was collected on 1400 patients over 12 years at a single institution. The data was analyzed evaluating SRS upfront as an only treatment or as salvage treatment following whole brain radiation with similar outcomes. This data may of use when evaluating patients with brain metastasis to help determine the most appropriate therapy

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