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Clinical Investigation

Predictors of Survival in Contemporary Practice After Initial Radiosurgery for Brain Metastases

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Summary

This study evaluated predictors of survival in a single-institution patient cohort treated initially only with stereotactic radiosurgery (SRS) for newly diagnosed brain metastases (BM). On multivariate analysis, extracranial disease, total tumor volume, age, and diagnosis-specific graded prognostic assessment emerged as statistically significant predictors of survival, while number of BM was not predictive of survival. We propose that future prospective studies should

Purpose: The number of brain metastases (BM) is a major consideration in determining patient eligibility for stereotactic radiosurgery (SRS), but the evidence for this popular practice is equivocal. The purpose of this study was to determine whether, following multivariate adjustment, the number and volume of BM held prognostic significance in a cohort of patients initially treated with SRS alone.

Methods and Materials: A total of 251 patients with primary malignancies, including non-small cell lung cancer (34%), melanoma (30%), and breast carcinoma (16%), underwent SRS for initial treatment of BM. SRS was used as the sole management (62% of patients) or was combined with salvage treatment with SRS (22%), whole-brain radiation therapy (WBRT; 13%), or resection (3%). Median follow-up time was 9.4 months. Survival was determined using the Kaplan-Meier method. Cox regression was used to assess the effects of patient factors on distant brain failure (DBF), local control (LC), and overall survival (OS).

Results: LC at 1 year was 94.6%, and median time to DBF was 10 months. Median OS was 11.1 months. On multivariate analysis, statistically significant predictors of OS were presence of extracranial disease (hazard ratio [HR], 4.2, $P<.001$), total tumor volume greater than 2 cm^3 (HR, 1.98; $P<.001$), age $\geq$60 years (HR, 1.67; $P=.002$), and diagnosis-specific graded prognostic assessment (HR, 0.71; $P<.001$). The presence of extracranial disease was a statistically significant predictor of DBF (HR, 2.15), and tumor volume was predictive of LC (HR, 4.56 for total volume >2 cm^3). The number of BM was not predictive of DBF, LC, or OS.

Conclusions: The number of BM is not a strong predictor for clinical outcomes following initial SRS for newly diagnosed BM. Other factors including total treatment volume and systemic

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emphasize total treatment volume to facilitate appropriate use of SRS.

disease status are better determinants of outcome and may facilitate appropriate use of SRS or WBRT. © 2012 Elsevier Inc.

Introduction

Nearly 30% of cancer patients will develop brain metastases (1). As systemic treatments provide more durable disease control outside of the blood-brain barrier, intracranial disease control becomes proportionately more important. Whole-brain radiation therapy (WBRT) has been a mainstay of treatment for sterilizing the entire brain but is also associated with adverse neurocognitive sequelae (2). An emerging treatment paradigm is the implementation of initial stereotactic radiosurgery (SRS) in select patient populations in order to provide excellent local control (LC) of metastatic lesions while avoiding the adverse effects of WBRT (3).

Unfortunately, selection criteria for triage between initial SRS and WBRT are poorly defined. Recently published American Society for Radiation Oncology evidence-based guidelines on management of newly diagnosed brain metastases report that patients presenting with multiple brain metastases (all less than 3-4 cm) have treatment options including radiosurgery alone, WBRT with radiosurgery boost, or WBRT alone (4). None of these 3 options has been shown to offer a significant survival advantage over the others. The reality is that our current practice is rooted in historical precedent and technical limitations of first generation radiosurgical systems rather than strong clinical evidence. Traditionally, a total lesion number of 3-4 or fewer has been used as a clinical rule of thumb for SRS eligibility (3). However, multiple recent reports have suggested that prognostic features, including total tumor volume, offer more powerful prognostic information in the modern era (5-10).

Cancer incidence is expected to increase in the coming years due to demographic trends and the dispersion of screening technologies. In light of the urgent need to determine valid clinical variables for assessing patient prognosis and assigning appropriate therapy in this population, we analyzed a large cohort of patients with brain metastases treated in a contemporary setting with SRS alone. Specifically, multiple patient and tumor characteristics were analyzed in multivariate fashion to determine their prognostic relevance with regard to distant brain failure (DBF), LC, and overall survival (OS).

Methods and Materials

Patient selection

After receiving approval from our Institutional Review Board, we retrospectively identified all patients who underwent Gamma Knife radiosurgery for brain metastases between June 2009 and March 2010 at our institution. Exclusion criteria were previous craniotomy and WBRT. Clinical information was abstracted from our in-house electronic medical record system. Metastasis volume for each lesion was determined from physician-defined contours and collected from the treatment planning software (GammaPlan, Elekta, Stockholm, Sweden).

Radiosurgery and clinical surveillance

All radiosurgery candidate cases were discussed in a weekly multidisciplinary conference prior to assignment to SRS or WBRT. Magnetic resonance imaging (MRI) studies of the brain were performed with a GE Healthcare (Milwaukee, Wisconsin) MRI machine operating at 1.5 T following application of a Leksell invasive stereotactic head frame for rigid head fixation on the day of SRS. Axial postcontrast 3-dimensional fast spoiled gradient echo (3D FSPGR) images (1-mm-slice thickness, 1-mm spacing) were obtained following administration of intravenous MultiHance ((gadobenate dimeglumine) injection Bracco Diagnostics, Milan, Italy) at the recommended dose of 0.1 mmol/kg (0.2 mL/kg). The prescription dose was determined by the volume of the lesion as outlined in Radiation Therapy Oncology Group guidelines (11). The prescription isodose contour was typically the 50% isodose line. A radiation oncologist and neurosurgeon collaborated to contour all targets and define prescription parameters.

Patients were typically seen after 4 weeks and then every 3 months and underwent contrast-enhanced neuroimaging at each visit. If local or distant failure was diagnosed, patients underwent salvage therapy with neurosurgery, repeated SRS, or WBRT, based on their disease and performance status. The last clinic visit or date of contact was used for right-censoring for patients alive at the time of analysis. Median follow-up for all patients was 9.4 months, while median follow-up for survivors was 21 months.

Statistical analysis

Data analysis was performed using Stata/MP version 12.0 statistical software (STATA 12.1; StataCorp., College Station, TX). The Pearson chi-squared test was used to assess measures of association in frequency tables. The survival function was carried out using Kaplan-Meier estimates. The log-rank test was used to assess the equality of the survivor function across groups. The equality of means for continuous variables was assessed using the t test. A P value of .05 or less was considered statistically significant. Statistical tests were based on a 2-sided significance level. The Cox proportional hazard model was used for multivariate analysis to assess the effects of patient, tumor, and other predictor factors of significance on the end points. The estimated hazard ratio is reported. The Wald test was used to assess the role of covariates in the model. We used the Schoenfeld global test to determine the proportional hazards assumption in the Cox proportional hazards model.

Results

Patient characteristics

A total of 251 patients with 542 brain metastases fit our inclusion criteria. Baseline patient characteristics are listed in Table 1. A total of 223 (88.8 %) patients had initial SRS treatment delivered

Table 1 Patient characteristics

Characteristic	Number of patients (%)
Age	
≥60	124 (50%)
Median	59.6 (range: 15.7-93.4)
Gender	
Male	121 (48%)
KPS	
≥80	116 (46%)
Baseline RPA class	
1	24 (10%)
2	216 (86%)
3	11 (4%)
Baseline DS-GPA class	
0-0.5	7 (3%)
1	33 (13%)
1.5	25 (10%)
2	63 (25%)
2.5	14 (6%)
3	68 (27%)
3.5-4	41 (16%)
Primary tumor	
Melanoma	74 (29%)
Non-small cell lung	85 (34%)
Breast (ductal)	40 (16%)
Renal	19 (8%)
Other	33 (13%)
Extracranial disease	
Yes	199 (27%)
Unknown	22 (9%)

Abbreviations: DS-GPA = diagnosis-specific graded prognostic assessment; KPS = Karnofsky performance status; RPA = recursive partitioning analysis.

through the use of a Leksell Gamma Knife (Perfexion model), and 28 patients had their first SRS treatment delivered using a linear accelerator-based system before the implementation of Gamma Knife at our institution in June of 2009. Salvage SRS in these 28 patients was performed using Gamma Knife. SRS was used as the sole treatment for brain metastases in 61% of the patients. Treatment characteristics are listed in Table 2.

Overall survival

Median survival of all patients was 11 months. Survival by recursive partitioning analysis (RPA) class was 38.8 months for class 1, 9.4 months for class 2, and 2.8 months for class 3. Univariate analysis of relevant patient characteristics was performed, and results are shown in Table 3. Number of brain lesions at presentation was not a statistically significant predictor of OS as a continuous variable. On univariate analysis, cutpoints of 2, 3, and 4 brain lesions were statistically significant, as were the volumes of the biggest brain lesions and the total volume of all lesions. On multivariate analysis, four factors were found to be statistically significant predictors of OS: (*1*) presence of extracranial disease at the time of SRS with hazard ratio (HR) of 4.2; (*2*) total tumor volume of >2 cm^3 with HR of 1.98; (*3*) age greater than 60 years with HR of 1.67; and (*4*) baseline diagnosis-specific graded prognostic assessment (DS-GPA) (12) with HR of 0.71

Table 2 Treatment characteristics

Characteristic	Median (range)
Total tumor volume (cm^3)	0.89 (0.03-22.9)
Largest single site volume (cm^3)	0.66 (0.03-21.9)
Number of metastases	2 (1-9)
Dose (Gy)	
All histologies	20 (8-25)
NSCLC	20 (14-24)
Melanoma	20 (15-24)
Breast	20 (8-24)
Salvage therapy	Number of patients (%)
None	155 (61%)
Neurosurgery	4 (2%)
WBRT	31 (12%)
SRS	56 (22%)
Neurosurgery and SRS	3 (1%)
Neurosurgery and WBRT	1 (<1%)
Unknown	1

Abbreviations: SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

(Table 4). Kaplan-Meier estimates plotted for OS as a function of total treatment volume are shown in Fig. The traditional selection criterion of four or more brain metastases at presentation was not a statistically significant predictor of OS on multivariate analysis.

The proportional hazards assumption was not violated for any of the models. The global test of proportionality yielded a nonsignificant *P* value for OS of .80. Additionally, there was no correlation observed between DS-GPA and the number of treated lesions ($R=-0.4146$). A correlation coefficient with an absolute value of 0.8 or higher is usually considered influential in a model.

Local control

The 1-year LC rate was 94.6%. One-year LC rate for lesions measuring ≥2 cm^3 was 87.3% compared to smaller lesions, which had 1-year LC of 96.3% (log rank, $P<.0001$). Of the 13 patients with local failure, 6 patients were treated with neurosurgery, 2 patients with WBRT, 1 patient with SRS, and 4 patients received systemic therapy.

On multivariate analysis, total tumor volume of greater than 2 cm^3 was a statistically significant predictor of worse LC (HR 4.56 [1.32-15.74, 95% Confidence Interval]) (Table 3). Interestingly, better DS-GPA was a statistically significant predictor for worse local control ($P=.05$).

Distant brain failure

Median time to DBF was 10 months, and 1-year distant brain control rate was 45%. The most common modalities for salvage were additional SRS (47%) and WBRT (22%).

On both univariate and multivariate analyses, only the presence extracranial disease was associated with DBF ($P=.01$) (Table 4). The number of intracranial metastases was not a statistically significant predictor of distant brain control regardless of whether it was included in the model as a continuous variable or any combination of categorical variables listed in Table 3.

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Table 3 Univariate cox regression analysis for overall survival

Variable	HR	*P* value	95% CI	Comparison group
Total volume	1.10	<.001	1.06-1.14	Continuous
Total volume >2 cm^3	2.07	<.001	1.50-2.85	Total treatment volume ≤2
Total volume >3 cm^3	2.16	<.001	1.53-3.04	Total treatment volume ≤3
Max volume	1.15	<.001	1.10-1.21	Continuous
Max volume >2 cm^3	1.98	<.001	1.43-2.76	Max treatment volume ≤2
Max volume >3 cm^3	2.20	<.001	1.55-3.14	Max treatment volume ≤3
Number of sites treated	0.99	.603	0.97-1.02	Continuous
2	1.42	.070	0.97-2.07	1 site
3	1.70	.018	1.10-2.65	1 site
≥4	2.34	.001	1.43-3.84	1 site
≥3	1.65	.003	1.18-2.31	1-2 sites
≥2	1.64	.003	1.18-2.28	1 site
Male gender	1.18	.280	0.87-1.61	Female
Age	1.01	.026	1.00-1.03	Continuous
Age ≥60	1.58	.004	1.16-2.16	<60
Baseline RPA	3.61	<.001	2.28-5.72	Continuous
2	4.51	<.001	1.99-10.22	0-1
3	13.24	<.001	4.66-37.56	
Baseline DS-GPA	0.61	<.001	0.51-0.71	Continuous
≥2	0.33	<.001	0.24-0.46	≤1.5
Baseline KPS	0.95	<.001	0.93-0.96	Continuous
Baseline KPS 90-100	0.44	<.001	0.32-0.61	≤80
Extracranial disease	4.31	<.001	2.11-8.81	No

Abbreviations: CI = confidence interval; DS-GPA = diagnosis-specific graded prognostic assessment; KPS = Karnofsky performance status; RPA = recursive partitioning analysis.

Discussion

SRS allows delivery of a precisely localized dose of radiation to a brain metastasis while sparing surrounding normal brain tissue (13). In some patients, this strategy offers LC comparable to or better than alternative therapies including surgery and WBRT. Additionally, SRS avoids the invasiveness and postoperative recovery required by resection and is believed to reduce the cognitive impairment associated with WBRT (2, 14-18). Given these characteristics, there is currently strong enthusiasm for broad adoption of SRS, but it is nonetheless necessary to select proper candidates for safe and effective use of this technology. Unfortunately, evidence to guide SRS adoption is currently sparse, and randomized controlled trials are available only in the setting of 1-4 metastases (4, 19-22).

Consensus recommendations have typically focused on using an arbitrary number of lesions as a criterion for SRS eligibility (8, 23). As such, patients with 4 or more brain metastases are typically treated with WBRT rather than SRS (20, 21, 24). Two considerations should make us question this clinical dogma. First, early use of SRS occurred in an era during which intracranial staging was done with computed tomography (CT). Because of the relatively low sensitivity of CT scanning, patients with more than 3 brain metastases were assumed to have additional occult metastases, and WBRT was felt to be the most sensible option for avoiding DBF (3). A second historical underpinning for current practice is that patients with brain metastases were categorized as having very grim prognoses, so the cognitive impairment associated with WBRT was underemphasized, given that patients were unlikely to live long enough to experience this adverse effect. This fatalistic approach to therapeutic decision making is less convincing now in the era of more efficacious chemotherapy regimens and targeted agents. In fact, survival was greater for each RPA category in our present study than that achieved by patients in the original RPA publication (25).

To investigate the importance of lesion number, we sought formally to identify prognostic factors for DBF, LC, and OS for 251 patients with brain metastases who underwent treatment with initial SRS. Importantly, all of these patients were treated in a contemporary period during which the above-described historical considerations were of low relevance. In our multivariate model, neither DBF nor LC was associated with the presence of 4 or more brain lesions at presentation. This finding, which challenges the traditional decision for triage between SRS and WBRT, held regardless of whether the number of lesions was analyzed categorically or as a continuous variable. Instead, DBF was most strongly associated with the presence of extracranial disease. This suggests that an active primary tumor, which may act as a source of distant seeding or as a marker for the absence of systemic disease control, is the most reliable predictor of risk for distant brain failure.

Patients with larger total intracranial tumor volume were less likely to achieve LC with SRS, and OS was likewise influenced by total volume in addition to systemic factors such as the presence of extracranial disease, older age, and lower DS-GPA. Notably, the

Table 4 Multivariate analysis for overall survival, local control, and distant brain control

Variable	Overall survival			Local control			Distant brain control			Comparison group
	HR	*P* value	95% CI	HR	*P* value	95% CI	HR	*P* value	95% CI	
Total lesion volume >2	1.98	<.001	(1.4-2.81)	4.56	.016	(1.32-15.74)	0.67	.10	(0.42-1.08)	Total treatment volume ≤2
Age ≥60 (y)	1.67	.002	(1.2-2.33)	0.89	.85	(0.26-3.06)	1.25	.25	(0.86-1.83)	<60 y
Baseline DS-GPA	0.71	<.001	(0.59-0.85)	2.33	.05	(1.02-5.30)	1.01	.90	(0.82-1.24)	Continuous
≥4 lesions	1.41	.17	(0.86-2.32)	4.01	.13	(0.66-24.42)	1.02	.97	(0.5-2.08)	1-3 sites
Extracranial disease	4.20	<.001	(2.04-8.68)	0.80	.72	(0.24-2.71)	2.15	.011	(1.19-3.9)	No

Abbreviations: CI = confidence interval; DS-GPA = diagnosis-specific graded prognostic assessment; HR = hazard ratio.

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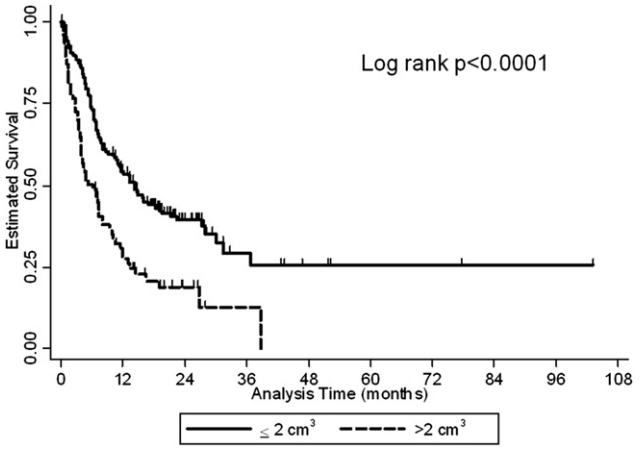

Fig. Overall survival by treatment volume (cut point, 2 cm^3).

number of lesions was again not prognostic for either of these outcomes. Whether total tumor volume predicts for poor treatment response to SRS or simply acts as a prognostic marker for aggressive and uncontrolled disease is currently a matter of controversy. At our institution, LC for tumors larger than 3 cm^3 was promising with a rate greater than 80% at 1 year, which suggests to us that treatment failure in larger lesions is unlikely to account fully for the significance of total treatment volume.

Interestingly, better baseline DS-GPA was a statistically significant predictor for worse local control. Although this could be a statistical anomaly, a plausible explanation is the decline in LC over the longer lifetime enjoyed by patients with better DS-GPA. Increased local failure over time has been demonstrated in several trials (2, 11, 22).

The superiority of treatment volume over lesion number for predicting outcomes is present not only in our study but in several other recent series. A Japanese multi-institutional prospective study (JLGK0901) is currently investigating the role of Gamma Knife radiosurgery for patients with 1-10 BM without prophylactic WBRT. A preliminary retrospective study of patients who met the JLGK0901 inclusion criteria has reported lack of prognostic significance for the number of BM (6). Bhatanagar et al (8) evaluated prognostic factors for patients who were treated with SRS for four or more brain metastases and found that total tumor volume was significantly associated with risk of death, whereas number of metastases was not. In a study of breast cancer metastases, Kondziolka et al (5) demonstrated that lesion size <3 cm^3 was associated with better survival on multivariate analysis. Likewise Matsunaga et al (26) found on multivariate analysis that the number of treated sites was not significantly associated with survival beyond a single lesion. Based on these experiences, we hypothesize that total tumor volume is a better determinant for patient stratification than lesion number.

Our study is retrospective and has important limitations. Heterogeneity with regard to primary diagnosis and patient factors limits the ability to generalize our results to specific patient populations. Nonetheless, we note that this study represents one of the largest modern series of SRS treatment for patients with brain metastases and that our study design reflects the clinical reality of providing triage to patients with brain metastases by using factors other than histology. A second limitation is that the number of patients with 4 or more lesions may not have provided adequate power to detect a statistically significant association with outcomes. However, our findings were unchanged when lesion number was entered into our model as a continuous variable.

Another potential criticism of this study is that the number of brain metastases is actually a component of the DS-GPA rubric for all cancer diagnoses except breast and gastrointestinal malignancies. Given that DS-GPA is highly significant in our multivariate analysis, the value of the number of metastases as an independent variable may be lost. To ensure that the correlation between these 2 variables did not influence our results, we performed the global test of proportionality and a correlation assessment between covariates. None of these statistical tests were violated. Therefore, results of the multivariate analysis suggest that in our series, the number of brain metastases was not an important prognostic factor, either alone or as part of DS-GPA.

Conclusions

In summary, our analysis represents one of the largest experiences with SRS in the treatment of brain metastases in the modern era and demonstrates that categorization of patients into bins of 1-3 or $\geq$4 lesions does not predict for LC, DBF, and OS. Therefore, the popular practice of directing patients with 4 or more lesions to treatment with WBRT alone is not supported by our findings. We assert that the historical underpinnings for this practice may not hold true in contemporary practice: MRI has proven to be a highly sensitive test for determining the true extent of intracranial disease, and the disregard of cognitive decline after WBRT is problematic in light of longer patient survival. Future prospective studies should emphasize total tumor volume rather than, or perhaps in addition to, lesion number for therapeutic approach.

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