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Clinical Investigation: Metastases

Prognostic Factors for Survival in Patients Treated With Stereotactic Radiosurgery for Recurrent Brain Metastases After Prior Whole Brain Radiotherapy

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Summary

Prognostic factors for survival were evaluated in patients with brain metastases (BM) treated with salvage stereotactic radiosurgery (SRS) after prior whole brain radiotherapy (WBRT). Favorable parameters included age <50 years, smaller total target volume, and longer interval from WBRT to SRS among breast cancer patients; controlled primary, KPS ≥70, and fewer BMs for non-small cell lung cancer; and smaller total target volume for melanoma. No cutoff was found for number of BMs above which salvage SRS should not be offered.

Purpose: To evaluate prognostic factors for survival after stereotactic radiosurgery (SRS) for new, progressive, or recurrent brain metastases (BM) after prior whole brain radiotherapy (WBRT).

Methods and Materials: Patients treated between 1991 and 2007 with Gamma Knife SRS for BM after prior WBRT were retrospectively reviewed. Potential prognostic factors were analyzed overall and by primary site using univariate and stepwise multivariate analyses and recursive partitioning analysis, including age, Karnofsky performance status (KPS), primary tumor control, extracranial metastases, number of BM treated, total SRS target volume, and interval from WBRT to SRS.

Results: A total of 310 patients were analyzed, including 90 breast, 113 non−small-cell lung, 31 small-cell lung, 42 melanoma, and 34 miscellaneous patients. The median age was 56, KPS 80, number of BM treated 3, and interval from WBRT to SRS 8.1 months; 76% had controlled primary tumor and 60% had extracranial metastases. The median survival was 8.4 months overall and 12.0 vs. 7.9 months for single vs. multiple BM treated ($p = 0.001$). There was no relationship between number of BM and survival after excluding single-BM patients. On multivariate analysis, favorable prognostic factors included age <50, smaller total target volume, and longer interval from WBRT to SRS in breast cancer patients; smaller number of BM, KPS >60, and controlled primary in non−small-cell lung cancer patients; and smaller total target volume in melanoma patients.

Conclusions: Among patients treated with salvage SRS for BM after prior WBRT, prognostic factors appeared to vary by primary site. Although survival time was significantly longer for patients with a single BM, the median survival time of 7.9 months for patients with multiple BM seems sufficiently long for salvage SRS to appear to be worthwhile, and no evidence

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was found to support the use of a cutoff for number of BM appropriate for salvage SRS.
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Keywords: Stereotactic radiosurgery, Brain metastases, Salvage, Prognostic factors, Gamma knife

Introduction

With advances in imaging and in the management of brain metastases (BM) over the past few decades, much has been written about treatment results and prognostic factors in patients with newly diagnosed BM (1–5). However, there is much less information about prognostic factors in patients who are offered salvage therapy after prior whole brain radiotherapy (WBRT), the most common initial treatment for BM (6, 7). Treatment options for recurrent BM include repeat WBRT (7–10), surgery, stereotactic radiosurgery (SRS) (11–13), and chemotherapy (14). It is our impression that the most common salvage treatment for BM is SRS. Obviously, these are selected patients, who must have survived long enough to suffer a recurrence and must have favorable enough prognosis and performance status to have been referred and accepted for salvage SRS, but there is probably less selection bias for SRS than for surgery.

Having recently evaluated prognostic factors among patients treated with Gamma Knife SRS (Leksell Gamma Knife, Elekta, AB, Stockholm, Sweden) for newly diagnosed BM (15), the present retrospective study was undertaken to evaluate prognostic factors in patients treated with Gamma Knife SRS at our institution for "recurrent" (new, progressive, or recurrent) BM after prior WBRT, and to determine if there were subsets of patients for whom median survival time (MST) was so short that it may not make sense to offer salvage SRS.

Methods

Study inclusion and exclusion criteria

This study included adults treated with Gamma Knife SRS at the University of California, San Francisco (UCSF) 1991–2007 for recurrent BM after previous WBRT. All patients who undergo Gamma Knife SRS are entered prospectively into a Gamma Knife database; the present study specifically excluded patients who were identified in this database as having been treated for "newly diagnosed" BM (*e.g.*, with WBRT plus SRS boost or SRS alone initially), even if they went on to later have SRS for recurrent BM. Newly diagnosed patients were included in our previous analysis of prognostic factors (15). Other exclusion criteria included prior SRS, age <18 years, and prior prophylactic WBRT.

Patient selection

Candidates for SRS were referred by medical oncologists, radiation oncologists, or neurosurgeons at UCSF or in surrounding communities and reviewed at a weekly multidisciplinary conference attended by one or more neurosurgeons, radiation oncologists, neuroradiologists, and Gamma Knife coordinator. Patients accepted for Gamma Knife SRS for recurrent BM had Karnofsky performance status (KPS) of at least 70, BM $\leq$4 cm in diameter, $\leq$2 BM 3–4 cm diameter, and no evidence of leptomeningeal disease. There was no set cutoff regarding number of BM.

All patients provided informed consent for treatment, and this retrospective study was approved by our institutional review board.

Radiosurgery technique

All SRS was performed using a Leksell Gamma Knife (16): model U between 1991 and July 1998, model B between September 1998 and 2001, model C between 2002 and October 2007, and the Perfexion model beginning in November 2007. After fixation of a Leksell stereotactic frame under local anesthesia, patients were imaged with gadolinium-enhanced magnetic resonance imaging (MRI) using single-dose contrast before mid-1994 and triple-dose contrast thereafter. The few patients with a contraindication to MRI were imaged with contrast-enhanced computed tomography. Targets were outlined without added margin and one or more isocenters were planned to conformally encompass each target. Prescribed doses ranged from 15 to 20 Gy in 91% of patients and 97% of brain metastases. Dexamethasone, 10 mg, was given intravenously on the day of SRS. Patients who were not on steroids before SRS were not started on a course of steroids unless they were found to have symptomatic brain edema; those who were on steroids were given a schedule to taper, beginning 4–7 days after SRS. Patients were discharged to home after a short observation period.

Follow-up

It was recommended that patients undergo brain MRI every 3 months and send the imaging for review at the weekly radiosurgery conference. Patients followed at UCSF had imaging and clinical notes available on computerized medical imaging and information systems. Dates of death were obtained from Social Security death records.

Statistical analyses

Survival was measured from the date of SRS until death or last clinical or imaging follow-up, and actuarial survival was calculated using the Kaplan-Meier method. For univariate and multivariate proportional hazards models, parameters analyzed for possible influence on survival time included age at the time of SRS (<65 vs. ≥65 years, the age cutoff used in the Radiation Therapy Oncology Group recursive partitioning analysis) (1), KPS (<70 vs. ≥70), control of the primary tumor (no = 0; yes = 1), known extracranial metastases (no = 0; yes = 1), interval from

WBRT until SRS by quartile, total target volume at the time of SRS by quartile, and number of BM treated with SRS (1 = 1; 2−3 = 2; 4−6 = 3; ≥7 = 4). Primary histology was categorized as breast, non−small-cell lung, small-cell lung, melanoma, and other. In addition to the analyses including all histologies, subgroup analyses were conducted for the histologies with more than 40 patients. In the case of breast cancer patients, age <50 years vs. ≥50 years, a historical cutoff to separate premenopausal from postmenopausal patients, was also analyzed and KPS was not analyzed because only 2 patients had KPS <70. Cox proportional hazards analyses were performed using Stata 10 software (StataCorp LP, College Station, TX). For multivariate analyses, backwards selection of variables was performed. Parameters with a significance level >0.2 were removed from the model. No attempt was made to adjust for multiple comparisons. Where sample sizes permitted, interaction terms were included in supplementary multivariate analyses to determine the likelihood that these differences were due to chance. Spearman's rank correlation coefficient was calculated to ensure sufficient independence between total target volume and number of BM treated to permit inclusion of both parameters together in multivariate and recursive partitioning analyses (Spearman's rho = 0.140 for continuous variables and 0.134 for binned variables). A recursive partitioning analysis was also performed using classification and regression tree software (CART version 6.0, Salford Systems, San Diego, CA) with the exclusion of 7 patients lost to follow-up immediately after SRS. The program was constrained to have a minimum final node size of 20 patients. Tenfold cross-validation was used. To allow for censoring, the method of martingale residuals described by Therneau *et al.* was used (17). Prognostic variables were not categorized before this analysis (*e.g.*, age was included as a continuous variable). Patients were grouped into nodes by the CART algorithm. The log−rank test is presented to provide information on the degree of difference in survival time based on each split.

Results

Patient characteristics and treatment parameters

Of 2,821 patients treated with Gamma Knife SRS at UCSF between 1991 and 2007, 1,033 were treated for BM including 657 patients with newly diagnosed BM and 376 with "recurrent" (recurrent, progressive, or new) BM after prior therapy. Of the 376 patients treated with SRS at the time of recurrence, 44 patients who did not receive previous WBRT were excluded; their sole prior treatment for BM had been surgery in 27 patients, partial brain RT in 9, SRS at other institutions in 5, and chemotherapy specifically for BM in 3 patients. For this analysis, 22 additional patients were also excluded: 19 patients who had undergone prior SRS at outside institutions, 2 patients whose previous WBRT had been prophylactic, and 1 pediatric patient. This left a total of 310 patients for analysis, 204 of whom had received prior WBRT only, and 106 of whom had undergone WBRT and surgery (resection of one or more BM in 94 patients and biopsy in 12 patients).

Prior WBRT dose was unknown in 33 patients and ranged from 19.8 to 60 Gy in the remaining patients, with only 10 patients having received <30 Gy and 10 patients having received >45 Gy. The most common WBRT regimens included 30 Gy in 10 fractions (77 patients), 35−40 Gy at 2.5 Gy per fraction (39 patients), 40 Gy in 20 fractions (24 patients), and 45 Gy in 25 fractions (11 patients).

Patient characteristics and SRS treatment parameters are summarized in Table 1. The three largest subpopulations by primary site were breast (90 patients), lung (144 patients), and melanoma (42 patients); 34 patients had renal, colorectal, unknown, or other primary sites. For all primary sites combined, the median age at the time of salvage SRS was 56 years and KPS 80; 76% of patients had controlled primary tumors and 40% had

Table 1 Patient characteristics and treatment parameters

Parameter	Breast (n = 90)	Non-small Cell Lung (n = 113)	Melanoma (n = 42)	All patients* (n = 310)
Number (%) with prior brain surgery	23 (26%)	42 (37%)	20 (48%)	106 (34%)
Age at SRS (y), median (range)	51 (25−70)	58 (36−85)	47 (25−77)	56 (25−85)
Number (%) <65 [<50] years of age at SRS	84 (93%) [38 (42%)]	83 (73%)	36 (86%)	250 (81%)
KPS at SRS, median (range)	80 (50−100)	80 (50−100)	80 (50−100)	80 (50−100)
% of patients with KPS ≥70	88 (98%)	99 (88%)	37 (88%)	280 (90%)
Number of brain metastases treated, median (range)	4 (1−31)	3 (1−15)	3 (1−18)	3 (1−31)
Number (%) with 1	14 (16%)	36 (32%)	8 (19%)	76 (25%)
2−3	28 (31%)	37 (33%)	14 (33%)	102 (33%)
4−6	22 (24%)	19 (17%)	12 (29%)	72 (23%)
≥7 brain metastases treated with SRS	26 (29%)	21 (19%)	8 (19%)	60 (19%)
Number (%) with controlled primary	83 (92%)	71 (63%)	36 (86%)	236 (76%)
Number (%) without known extracranial metastases	20 (22%)	67 (59%)	6 (14%)	123 (40%)
Interval from WBRT to SRS (months), median (range)	9.8 (1.9−86.0)	8.2 (1.1−46.9)	4.0 (0.5−32.4)	8.1 (0.5−86.0)
Minimum prescribed SRS dose (Gy), median (range)	17.0 (7.5−20.0)	17.5 (8.0−20.0)	16.5 (12.0−20.0)	17.0 (7.5−20.0)
Maximum prescribed SRS dose (Gy), median (range)	19.0 (9.0−21.0)	18.5 (8.0−20.5)	19.0 (12.0−22.0)	18.5 (8.0−22.0)
Total target volume, median (range)	4.8 (0.3−30.9)	4.8 (0.2−54.4)	8.5 (0.1−33.0)	5.8 (0.1−54.4)
Total treated volume, median (range)	8.4 (0.6−39.7)	7.8 (0.4−80.3)	15.2 (0.5−43.1)	8.8 (0.4−80.3)

Abbreviations: KPS = Karnofsky performance score; SRS = stereotactic radiosurgery; WBRT = whole brain radiotherapy.
* This includes patients with miscellaneous and unknown primary tumor sites.

no known extracranial metastases. The median number of lesions treated was 3 (range, 1−31), minimum prescribed dose 17.0 Gy (range, 7.5−20.0 Gy; 91% at least 15 Gy), maximum prescribed dose 18.5 Gy, minimum isodose contour 50% (range, 30−81), total target volume 5.8 mL, and total volume encompassed by the prescription isodose lines 8.8 mL. The median, 75th percentile, and 95% percentile values of the number of BM treated were 2, 4, and 7 using the U model vs. 3.5, 7, and 14 using later Gamma Knife models.

All visible BM were treated with SRS in 78% of the patients. Reasons for not treating all visible metastases were categorized as favorable if the untreated lesions were smaller or stable since WBRT (n = 23) or tiny and indeterminate (3) vs. unfavorable reasons if the untreated lesions were too large (5), too numerous (16), physically out of reach (15), or if leptomeningeal disease was seen at the time of SRS (5). In many such "unfavorable" cases, patients had been accepted for SRS based on imaging showing fewer or smaller lesions and no evidence of leptomeningeal disease, and the treating team proceeded with SRS despite the new findings to palliate larger or symptomatic lesions or those in locations most likely to become symptomatic. Except for 1 patient with three of six metastases treated in 1991 shortly before image-based treatment planning software became available in early 1992, the total number of BM among the 16 cases of "too numerous" lesions ranged from 15 to >100 (median, 22).

Survival times

Dates of death were available for 285 of 310 patients (92%). Seven patients were lost to follow-up immediately after treatment. Follow-up in the remaining 18 censored patients ranged from 1.9 to 129.8 months (median, 9.6 months).

Median survival times are summarized in Table 2 for the total patient population and major primary sites, with break-downs by the major parameters evaluated for prognostic significance. Most subsets analyzed had a MST of at least 6 months. The MST for the entire study population was 8.4 months after SRS, 5.5 months for small-cell lung cancer, 7.2 months for melanoma, 8.1 months for non−small-cell lung cancer, and 11.4 months for breast cancer. Interestingly, history of extracranial metastases was insignificant overall and for each primary site analyzed.

Among breast cancer patients, significantly longer survival was associated with age <50 years ($p = 0.001$; HR = 2.36), smaller total target volume by quartile ($p = 0.009$; HR = 1.32), and longer interval from WBRT until SRS by quartile ($p = 0.002$; HR = 0.70). Estrogen receptor (ER) status was known in 78% of breast cancer patients, progesterone receptor (PR) status in 73%, and human epidermal growth factor 2 (HER2) over-expression status in 53%. There was no difference in survival by ER status (MST 10.2 vs. 11.4 months for 37 ER-negative vs. 33 ER-positive patients; $p = 0.51$), but MST was 5.2 vs. 15.7 months among 14 patients without vs. 34 with HER2 over-expression ($p = 0.17$).

The univariate prognostic factors for non−small-cell lung cancer patients included control of the primary tumor ($p = 0.001$; HR = 0.50) and number of BM treated, grouped as 1, 2−3, 4−6, or ≥7 ($p = 0.003$; HR = 1.29). The only prognostic factor for melanoma patients was smaller total target volume by quartile ($p = 0.004$; HR = 1.67), though analysis was limited by the fact that multiple other potential prognostic factor subsets contained only 5−6 patients.

The MST was 8.6 months among the 243 patients in whom all lesions were treated with SRS (including 16 patients [6.6%] who lived longer than 3 years) vs. 9.3 months among the 26 patients in whom the only untreated lesions were smaller or stable since WBRT or tiny and indeterminate (including 2 patients [7.7%] who lived longer than 3 years) ($p = 0.44$). The MST was 7.0 months if there was an unfavorable reason for not treating all lesions ($p = 0.03$ compared with the other two groups combined).

There was no attempt to analyze survival according to whether BM were new, progressive, or recurrent after prior WBRT; many patients would have had mixtures of these categories, this information was not scored prospectively for individual lesions, and in numerous cases, serial MRIs from before WBRT until SRS were not available to make this determination.

Regarding the issue of number of metastases appropriate for SRS, patients who received SRS to a single BM had a longer MST than those treated for multiple BM (12.0 vs. 7.9 months; $p = 0.001$). However, there was no clear trend toward shorter survival time with increasing number of BM beyond 2−3; MSTs were 7.9, 6.6, and 9.7 months and 1-year survival probabilities 30%, 19%, and 40% for 2−3, 4−6, or ≥7 BM treated with SRS, respectively ($p = 0.76$) (Table 2; Fig. 1). Among 20 patients with ≥12 BM, the MST was 9.6 months. Excluding patients with an unfavorable reason for not treating all lesions, the MSTs were 8.1, 7.2, and 9.7 months for 2−3, 4−6, or ≥7 BM treated ($p = 0.55$).

Multivariate analyses

Results of multivariate analyses are shown in Table 3. Prior surgery had little influence on survival and was not included in further analyses (MST 8.1 vs. 8.5 months without vs. with prior resection; $p = 0.13$). On backward stepwise multivariate analysis, longer survival was significantly associated with age <50 years ($p = 0.002$; HR = 2.24), smaller total target volume (p = 0.042; HR = 1.25) and longer interval from WBRT to SRS ($p = 0.009$; HR = 0.73) among breast cancer patients; smaller number of BM ($p = 0.003$; HR = 1.31) KPS ≥70 ($p = 0.004$; HR = 0.40), and controlled primary tumor ($p = 0.001$; HR = 0.48) among non−small-cell lung cancer patients; and smaller total target volume among melanoma patients ($p = 0.004$; HR = 1.67). In the overall analysis, which included histology as a possible factor, the most significant parameters included KPS ($p < 0.001$; HR = 0.46), primary tumor control ($p = 0.005$; HR = 0.66), and smaller total target volume by quartile ($p < 0.001$; HR = 1.22). Number of BM had a p value of 0.023 in the overall multivariate analysis but dropped out in a multivariate analysis excluding patients treated to a single BM. Again, presence vs. absence of known extracranial metastases was not found to have significant prognostic value.

Multivariate analyses were also performed excluding the 41 patients who had unfavorable reasons for failure to treat all BM with SRS, giving very similar results to the analyses for all patients (data not shown).

Looking at potential differences in prognostic factors by primary site, the two most important candidates included total target volume and number of BM treated. Interaction tests performed with each of these two parameters for breast and non−small-cell lung cancer patients (the two groups for whom there were sufficient cases) showed no interaction between site and total target volume quartile ($p = 0.37$) but there was a significant interaction between site and number of metastases ($p = 0.044$),

Table 2 Median survival times for various subgroups with Cox proportional hazards *p* values

Subgroup	Breast	Non-small cell Lung	Melanoma	All patients*
Overall (*n*)	11.4 (90)	8.1 (113)	7.2 (42)	8.4 (310)
Age <65 (*n*)	11.4 (84)	8.3 (82)	7.2 (36)	8.6 (250)
Age ≥65 (*n*)	− (6)	8.1 (30)	− (6)	7.6 (60)
p value	NS	0.20	NS	0.054
Age <50 (*n*)	12.2 (38)	−	−	−
Age ≥50 (*n*)	7.9 (52)			
p value	0.001			
KPS <70 (*n*)	− (2)	7.3 (14)	− (5)	5.8 (30)
KPS ≥70 (*n*)	11.6 (88)	8.3 (99)	7.2 (37)	8.6 (280)
p value	Invalid	0.11	NS	0.001
Primary uncontrolled (*n*)	13.4 (7)	5.7 (42)	− (6)	6.3 (74)
Primary controlled (*n*)	11.4 (83)	10.4 (71)	6.2 (36)	9.1 (236)
p value	NS	0.001	NS	0.001
No extracranial mets (*n*)	9.3 (20)	8.6 (67)	− (6)	8.1 (123)
Extracranial mets (*n*)	11.9 (70)	7.3 (46)	6.3 (36)	8.6 (187)
p value	NS	NS	NS	NS
Total target volume				
First quartile (≤2.6 mL) (*n*)	15.7 (27)	8.3 (31)	− (6)	11.1 (77)
Second quartile (2.62−5.7 mL) (*n*)	11.6 (22)	9.7 (29)	10.6 (10)	9.7 (77)
3rd quartile (5.8−11.8 mL) (*n*)	11.7 (20)	5.7 (29)	8.4 (10)	6.0 (78)
4th quartile (11.81−54.4 mL) (*n*)	8.0 (20)	9.9 (24)	4.7 (16)	7.4 (78)
p value	0.009	NS	0.004	<0.001
Number of brain metastases treated with SRS:				
1 (*n*)	17.4 (14)	11.6 (36)	12.6 (8)	12.0 (76)
2−3 (*n*)	9.1 (28)	8.1 (37)	8.4 (14)	7.9 (102)
4−6 (*n*)	8.7 (22)	6.0 (19)	7.2 (12)	6.6 (72)
7−31 (*n*)	13.4 (26)	8.7 (21)	6.0 (8)	9.7 (60)
p value	NS	0.003	0.15	0.006
Interval from WBRT to SRS:				
First quartile (*n*)	8.0 (14)	5.9 (28)	7.2 (22)	7.3 (77)
Second quartile (*n*)	7.0 (19)	8.1 (28)	8.0 (9)	7.0 (77)
Third quartile (*n*)	12.2 (28)	9.2 (28)	− (4)	9.1 (78)
Fourth quartile (*n*)	13.2 (29)	10.9 (29)	8.6 (7)	11.8 (78)
p value	0.002	0.13	NS	0.011
Interval from WBRT to SRS:				
≤6 months	7.8 (21)	7.4 (37)	7.6 (25)	7.4 (104)
>6 months	12.2 (69)	8.7 (76)	6.3 (17)	9.0 (206)
p value	0.001	NS	NS	0.13

Abbreviations: KPS = Karnofsky performance score; NS = not significant at a *p* value <0.20; SRS = stereotactic radiosurgery; WBRT = whole brain radiotherapy.

* This includes patients with miscellaneous and unknown primary tumor sites.

suggesting that the prognostic significance of number of BM may truly differ between breast and non−small-cell lung cancer patients.

Recursive partitioning analysis

Classification and regression tree (CART) analysis yielded total target volume ≤6.8 mL vs. >6.8 mL then single vs. multiple BM treated with SRS as the two principal recursive nodes, suggesting that total target volume is of more prognostic value than number of BM, and that number of BM beyond one was not of prognostic value (Fig. 2). Of note, even the two worst prognosis nodes had MSTs of 5.8−6.6 months.

Discussion

This study sought to evaluate the prognostic factors for patients treated with SRS as salvage therapy for new, progressive, or recurrent BM after prior whole-brain radiotherapy (with or without prior surgery) and to look for any major patient subsets with very short MST. Any interpretation of these results is limited by substantial selection bias, which is inherent to retrospective analyses. Any patient who is offered further treatment in the setting of recurrent BM is likely to have a good performance status and expected survival of more than a few months. Another limitation of this study is the inability to control potentially confounding factors, precluding determination of causality for

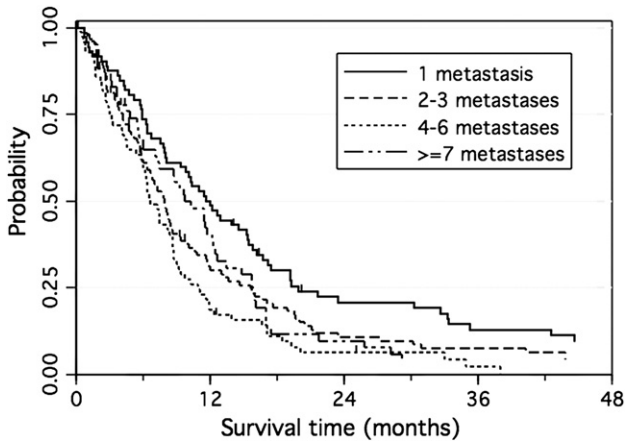

Fig. 1. Kaplan-Meier survival curve for patients with 1, 2−3, 4−6, and ≥7 brain metastases (BM) treated with salvage stereotactic radiosurgery. Patients treated for a single BM had a significantly longer median survival time than those treated for multiple BM (12.0 vs. 7.9 months; $p = 0.001$). Among patients with multiple lesions treated, there was no statistically significant trend toward shorter survival with increasing number of BM.

variables associated with survival time. Furthermore, the study was limited by the small size of some subpopulations, which may have affected both the results of the analyses as well as our interpretation, and there was no correction for multiple comparisons in calculating p values.

With these limitations in mind, associations were evaluated between survival time and age, KPS, primary tumor control, extracranial metastases, number of lesions treated with SRS, total target volume treated with SRS, and interval from WBRT until salvage SRS using univariate and backward stepwise multivariate Cox proportional hazards models. These results suggest that, in the setting of recurrent BM after previous WBRT, prognostic factors for patients undergoing salvage SRS may vary by primary site. This observation is in contrast to that of a recent study where primary tumor site did not appear to be associated with survival time in a similar clinical setting (6). This apparent contradiction may be due to differences in study population size; there were 90 breast cancer patients and 113 non−small-cell lung cancer patients as opposed to the 25 breast cancer and 53 non−small-cell lung cancer patients in the study by Chao *et al.* However, our analyses were also limited by small subpopulation sizes.

Chao *et al.* reported a MST of 9.9 months after SRS for recurrence after prior WBRT with or without prior surgery and/or SRS (6). This is slightly longer than the MST in the present study, which excluded patients treated with prior SRS. The primary prognostic factor in the study by Chao *et al.* was interval between WBRT and recurrence, with a MST of 6.8 vs. 12.3 months for first recurrence ≤6 vs. >6 months after WBRT ($p = 0.006$) (6). In the present study, the MST was 7.4 vs. 9.0 months for ≤6 vs. >6 months from WBRT to salvage SRS, with a MST of 11.8 months in the highest quartile group that had salvage SRS >14.5 months after WBRT.

The current results were also compared with those of a recent study at our institution that evaluated prognostic factors among patients with newly diagnosed BM treated with Gamma Knife SRS (15). That study found that prognostic factors varied significantly by primary site. Among breast cancer patients, the only important prognostic factor in the setting of newly diagnosed BM was primary tumor control (as opposed to time between WBRT and salvage SRS and total target volume by quartile and age <50 years in the present study, in which only 7 patients had uncontrolled primary tumor). Among lung cancer patients, the important prognostic factors among patients with newly diagnosed BM included age, history of extracranial metastases, and number of lesions treated (as opposed to KPS, primary tumor control, and number of lesions for patients with non−small-cell lung cancer in the present study). These comparisons suggest that prognostic factors may differ for patients with recurrent vs. newly diagnosed BM, though it is also quite possible that any apparent differences in prognostic factors may stem from differences in populations treated and small subgroups.

Table 3 Backward stepwise multivariate Cox proportional hazards analysis p values, hazard ratios, and 95% confidence intervals

Subgroup	Parameter	p value	HR	95% CI
Breast ($n = 90$)	Age (<50 vs. ≥50)	0.002	2.24	(1.36−3.71)
	Total target volume by quartile	0.042	1.25	(1.01−1.54)
	Interval from WBRT to SRS by quartile	0.009	0.73	(0.58−0.92)
Non−small-cell lung ($n = 113$)	Number of brain metastases (1 = 1; 2−3 = 2; 4−6 = 3; ≥7 = 7)	0.003	1.31	(1.10−1.56)
	KPS (<70 vs. ≥70)	0.004	0.40	(0.21−0.75)
	Primary controlled (no = 0; yes = 1)	0.001	0.48	(0.32−0.73)
Melanoma ($n = 42$)	Total target volume by quartile	0.004	1.67	(1.18−2.36)
All patients ($n = 310$)	Age (<65 vs. ≥65)	0.19	1.23	(0.90−1.68)
	KPS (<70 vs. ≥70)	<0.001	0.46	(0.31−0.69)
	Primary controlled (no = 0; yes = 1)	0.005	0.66	(0.49−0.88)
	Extracranial metastases (no = 0; yes = 1)	0.12	1.23	(0.95−1.59)
	Total target volume by quartile	<0.001	1.22	(1.09−1.37)
	Number of brain metastases (1 = 1; 2−3 = 2; 4−6 = 3; ≥7 = 7)	0.023	1.14	(1.02−1.28)
	Interval from WBRT to SRS by quartile	0.088	0.91	(0.82−1.01)
	Small−cell-lung primary (no = 0; yes = 1)	0.034	1.56	(1.03−2.34)

Abbreviations: CI = confidence interval; KPS = Karnofsky performance score; SRS = stereotactic radiosurgery; WBRT = whole brain radiotherapy.

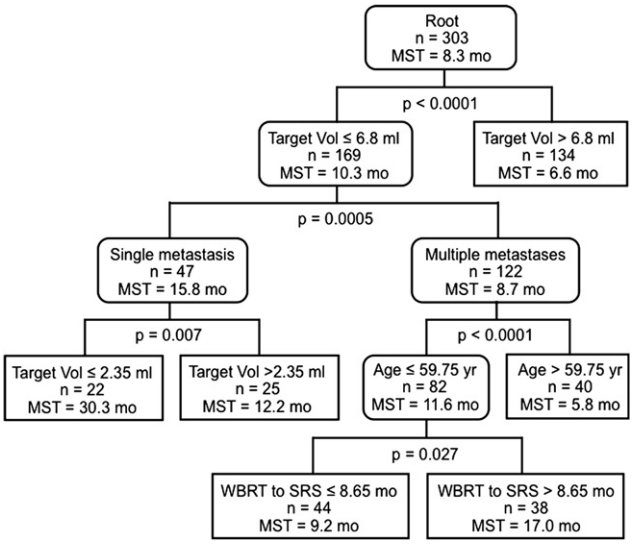

Fig. 2. Recursive partitioning analysis tree of the 303 patients who were not immediately lost to follow-up; the model was constrained to have a minimum final node size of 20 patients. The log−rank test was used to evaluate the degree of difference in survival times based on each split. MST = median survival time; n = number of patients in each node.

In our study, total target volume was a major prognostic factor, though even the patients in the highest total target volume quartile (range, 11.81−54.4 mL; median, 16.5 mL) had a MST of 7.4 months.

The number of BM treated was statistically significant for the study population as a whole and for patients with non−small-cell lung cancer but not for patients with breast cancer or melanoma. Historically, patients with a single metastatic brain lesion have lived longer than those with multiple lesions (18−20). In the current study, the MST was 12.0 vs. 7.9 months for single vs. multiple BM; $p = 0.001$). However, among patients with multiple BM, smaller number of BM was not associated with longer survival time; the MSTs were 7.9, 6.6, and 9.7 months for 2−3, 4−6, or ≥7 BM treated ($p = 0.76$). Within the range represented in this study including 60 patients with ≥7 BM and 20 patients with ≥12 BM treated, no evidence was found to argue for a rational cutoff value for number of lesions above which salvage SRS should not be offered. Further supporting this notion is our finding that in the recursive partitioning analysis of the entire patient population, the only split based on number of metastases was for 1 vs. >1 metastasis.

Finally, no major subgroup was found for which MST was very short (≤3 months). Unexpectedly, presence vs. absence of known extracranial metastases did not appear to be of prognostic value in these patients treated for recurrent BM.

Conclusions

Among the selected patients who received SRS for new, progressive, or recurrent BM after prior WBRT, the MST after SRS was 8.4 months overall. Prognostic factors appeared to vary by primary site. Although survival was significantly longer for patients with a single metastasis, the MST of 7.9 months for patients with multiple metastases seems sufficiently long for salvage SRS to appear to be worthwhile. No evidence was found for a cutoff value for number of BM appropriate for salvage SRS; total target volume appears to have more prognostic value than number of BM.

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