J Neurooncol (2016) 128:119–128
DOI 10.1007/s11060-016-2084-2

CLINICAL STUDY

Management patterns of patients with cerebral metastases who underwent multiple stereotactic radiosurgeries

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Received: 2 November 2015 / Accepted: 15 February 2016 / Published online: 7 March 2016

Abstract With escalating focus on cost containment, there is increasing scrutiny on the practice of multiple stereotactic radiosurgeries (SRSs) for patients with cerebral metastases distant to the initial tumor site. Our goal was to determine the survival patterns of patients with cerebral metastasis who underwent multiple SRSs. We retrospectively analyzed survival outcomes of 801 patients with 3683 cerebral metastases from primary breast, colorectal, lung, melanoma and renal histologies consecutively treated at the University of California, San Diego/San Diego Gamma Knife Center (UCSD/SDGKC), comparing the survival pattern of patients who underwent a single (n = 643) versus multiple SRS(s) (n = 158) for subsequent cerebral metastases. Findings were recapitulated in an independent cohort of 2472 patients, with 26,629 brain metastases treated with SRS at the Katsuta Hospital Mito GammaHouse (KHMGH). For the UCSD/SDGKC cohort, no significant difference in median survival was found for patients undergoing 1, 2, 3, or ≥4 SRS(s) (median survival of 167, 202, 129, and 127 days, respectively). Median intervals between treatments consistently ranged 140–178 days irrespective of the number of SRS(s) (interquartile range 60–300; p = 0.25). Patients who underwent >1 SRSs tend to be younger, with systemic disease control, harbor lower cumulative tumor volume but increased number of metastases, and have primary melanoma ($p < 0.001$, <0.001, <0.001, 0.02, and 0.009, respectively). Comparable results were found in the KHMGH cohort. Using an independent validation study design, we demonstrated comparable overall survival between judiciously selected patients who underwent a single or multiple SRS(s).

Keywords Brain metastasis · Repeat treatment · Stereotactic radiosurgery · Gamma knife surgery

Masaaki Yamamoto and Clark C. Chen are equal contributions as senior authors.

Electronic supplementary material The online version of this article (doi:10.1007/s11060-016-2084-2) contains supplementary material, which is available to authorized users.

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Introduction

Treatment paradigms for cerebral metastasis are of critical importance in the field neuro-oncology. While the actual incidence is unknown, it is estimated that 10–30 % of all cancer patients will develop cerebral metastases during the course of their diseases [1, 2], amounting to ~100,000–300,000 new cases annually in the United States.

Stereotactic radiosurgery (SRS) is the treatment of choice for patients suffering from limited number of

cerebral metastases that are not amenable to surgical resection [3]. However, up to half of all treated patients suffer from the development of metastasis outside of the region treated with SRS, requiring subsequent treatment [4, 5]. While multiple SRSs are routinely performed in this setting, emerging results suggested that the serial development of multiple brain metastases may be prognostic for poor survival [6]. In this context, some investigators have argued that whole brain radiation therapy (WBRT) warrants consideration, since patients with limited life expectancy are unlikely to suffer from the long-term deleterious effects of WBRT [7]. The argument is particularly poignant in the context of the increasing need to triage resources in health care [8].

Central to the resolution of this debate is the survival patterns of patients suffering from cerebral metastasis who underwent multiple SRSs. Unfortunately, limited data is available in this regard [9]. Here, we retrospectively analyzed survival outcomes of 801 patients with 3683 cerebral metastases consecutively treated at the University of California, San Diego/San Diego Gamma Knife Center (UCSD/SDGKC), comparing the survival pattern of patients who underwent a single (n = 643) versus multiple SRSs (n = 158). Results were validated in an independent cohort of 2472 patients with 26,629 cerebral metastases treated with SRS at the Katsuta Hospital Mito GammaHouse (KHMGH).

Methods

Patient cohort

We performed an Institutional Review Board (IRB) approved retrospective analysis of 1021 consecutive patients who underwent gamma-knife SRS for cerebral metastasis (1994–2011). We included patients with the five most common types of cerebral metastases by primary histology (breast, lung, colorectal, melanoma, and renal) in this analysis. For patients who underwent multiple SRSs, all patients included in this series underwent SRS for metastases distant to the lesion initially treated. We identified 801 unique patients, 158 of whom underwent multiple SRSs. If multiple lesions were treated during the same episode of care, this was considered a single SRS procedure; and multiple SRSs refers to patients who underwent subsequent episodes of care for newly developed lesions. All patients were referred for SRS by a radiation oncologist, medical oncologist, or neurosurgeon. In-house electronic medical record data were gathered, including age, gender, Karnofsky performance status (KPS), primary tumor histology, number of brain metastases, cumulative tumor volume, prior radiation treatment, and date of last follow-up. We accessed Social Security Master Death Files [10] to obtain patient death dates. The independent validation dataset was derived from 3640 consecutive patients with cerebral metastasis from primary breast, colorectal, lung, melanoma and renal histologies consecutively treated with SRS at the KHMGH from 1998 to 2013. We identified 2472 unique patients, 775 (31 %) of which underwent multiple SRSs.

For patients who underwent multiple SRSs, certain clinical variables, such as age, number of metastases, and cumulative tumor volume changed through clinical course; systemic disease status, KPS, and prior radiation treatment may also have changed. The information used for analysis was the one pertinent to the final radiosurgery. For instance, a patient who underwent SRS at age 33 and another at 34 would be classified as a 34 year-old patient who underwent two SRSs. Tumor characteristics and SRS parameters of this patient would be those associated with the second SRS.

All SRS candidates at UCSD and KHMGH were reviewed in a multidisciplinary tumor board. Patients who underwent recommended surgical resection were excluded from this analysis. In general, WBRT is reserved for patients undergoing palliative care, patients who cannot reliably follow-up with serial MRIs, patients whose intracranial tumor burden is prohibitive to SRS [11–13], and patients with miliary metastases. New contrast enhancing lesions with associated FLAIR signal abnormalities are generally treated. However, treatment strategies were individualized to the patient's general and oncologic condition after careful discussion of the risks and benefits of WBRT versus SRS.

Radiosurgery technique

MRI studies of the brain were performed with a GE Healthcare (Milwaukee, Wisconsin) MRI machine following application of a Leksell stereotactic head frame. Imaging was performed as thin-slice (1 mm) axial and coronal T1-weighted pre- and post-contrast MR sequences. The radiosurgery team consisting of a neurosurgeon, medical physicist and radiation oncologist then formulated treatment plans. The Leksell Unit model B was used before 2004 and the Unit model C (Elekta Instruments, Inc) was used thereafter. Dosimetric planning was performed with Elekta's Gamma Plan software. Prescription dose was delivered to the 50 % isodose line. In general, dose selection was consistent with Radiation Therapy Oncology Group (RTOG) 95-08 guidelines [14]. Additional parameters such as total number of metastases, tumor volume and prior or planned WBRT were also taken into consideration during dosimetric planning. The dose to the optic nerve was limited to 10 Gy. Dosing to the brainstem was limited

to 18 Gy. In the patients who had previously undergone WBRT, peripheral doses were decreased by 10–15 %. For each patient, all lesions were treated in a single setting. If the dose delivered to the various lesions differed, the reported dose represented an average of all metastases irradiated. The radiosurgery techniques used in the KHMGH validation cohort were described previously [15] and are largely analogous to the methods described above.

Statistical analysis

Patient characteristics were analyzed for differences between groups by the number of SRSs using one-way analysis of variance (ANOVA), Pearson Chi squared and independent samples Kruskal–Wallis tests. Next we determined survival patterns by analyzing interval days to final SRS and overall survival. We compared interval days to final SRS between groups by number of SRSs using independent samples Kruskal–Wallis tests. Days to final SRS was then log transformed for improved visualization given the wide range of the time intervals. Overall survival from time of final SRS treatment was estimated using the Kaplan–Meier method and compared by number of SRSs using the log-rank test [16]. Finally, a multivariate cox proportional hazards model was used to estimate hazard ratios and 95 % confidence intervals from time of final SRS controlling for age (≥65), KPS (≥70), number of metastases (3 or greater), cumulative tumor volume (>4 cc), systemic disease status, and primary tumor histology [17]. Each co-variable and corresponding cutoff, where applicable, was previously shown to be a mutually independent predictor of survival [18, 19].

All statistical tests were two-tailed and a p value <0.05 was considered significant. All statistical calculations were performed using R programming (version 3.1.1) and the survival package.

Results

Patient characteristics

Patient characteristics for the UCSD/SDGKC cohort are summarized in Table 1. 1021 SRS sessions were performed for 3683 metastases in 801 individuals with breast ($n = 172$, 21 %), colorectal ($n = 36$, 5 %), lung ($n = 376$, 47 %), melanoma ($n = 158$, 20 %) and renal ($n = 59$, 7 %) cancer. The mean age of the study population was 59 (SD = 13) and mean KPS was 80 (SD = 12). The median number of cerebral metastases per patient was 2 (range 1–5). The median cumulative tumor volume was 4 cc (range 1–8). Systemic control of primary disease was not achieved in the majority of the patients in this cohort (72 %). Most patients did not undergo WBRT (67 %) at any point of their clinical course.

Patient characteristics were analyzed based on whether they underwent multiple SRSs. Relative to the patients who underwent a single SRS, the multiple SRS patients were more likely to: (1) be younger ($p < 0.001$); (2) have achieved systemic disease control ($p < 0.001$); (3) suffer from metastases with smaller cumulative tumor volume ($p < 0.001$); (4) suffered larger number of cerebral metastases ($p = 0.02$), and 5) be more likely suffer from melanoma ($p = 0.009$).

Time between SRSs

For the UCSD/SDGKC cohort, the median intervals between treatments consistently ranged 140–178 days irrespective of the number of SRSs [interquartile range ('range') 60–300; $p = 0.25$, Fig. 1a]. For the patients who underwent two SRSs, the median time interval between the first and the second SRS was 178 days (range 112–293). For those patients who underwent three SRSs, the median time interval between the second and the third SRS was 154 days (range 84–300). For those patients who underwent ≥4 SRSs, the median time interval between the next to last SRS to the last SRS was 140 days (range 60–193). Given the wide range of time to final SRS, the data is also plotted on a log-scale (Fig. 1b).

Overall survival pattern

There were no significant differences in overall survival of patients who underwent a single or multiple SRS(s). The median overall survival of all patients following final SRS was 169 days (~5 months, 95 % CI 103–285 days), Fig. 2. The median overall survival of patients who underwent one SRS was 167 days (95 % CI 146–198 days). For patients undergoing two SRSs, the median survivals from date of last treatment was 202 days (95 % CI 146–284 days). For patients undergoing three SRSs, the median survivals from date of last treatment was 129 days (95 % CI 80–302 days). For patients who underwent ≥4 SRSs, the overall survival was 127 days (95 % CI 75 days, NA). The differences between these median survivals were not statistically significant ($p = 0.49$).

Multivariable analysis

A multivariable analysis was performed to determine whether the additional SRSs influence overall survival after correcting for pertinent clinical variables [19], including age, KPS, systemic disease control, the number of metastases, the cumulative tumor volume, and primary tumor

Table 1 Characteristics of UCSD/SDGKC patients with brain metastases undergoing multiple stereotactic radiosurgeries (SRSs)

Characteristic	Overall	1 SRS	2 SRSs	3 SRSs	≥4 SRSs	p value
Total patients [N (%)]	801 (100)	643 (80)	117 (15)	28 (3)	13 (2)	
Median interval days to final SRS (IQR)	161 (103–285)	–	178 (112–293)	154 (84–300)	140 (60–193)	0.25[a]
Median overall survival in days (95 % CI)	169 (149–195)	167 (146–198)	202 (146–284)	129 (80–302)	127 (75–NA)	0.49[b]
Age						
Mean (SD)	59 (13)	60 (13)	56 (13)	54 (11)	54 (15)	<0.001[c]
≥65 [N (%)]	296 (37)	257 (40)	32 (27)	5 (18)	2 (15)	
<65 [N (%)]	505 (63)	386 (60)	85 (73)	23 (82)	11 (85)	
Primary tumor histology						
Breast [N (%)]	172 (21)	132 (21)	31 (27)	7 (25)	2 (15)	0.009[d]
Colorectal [N (%)]	36 (5)	34 (5)	1 (1)	1 (4)	0 (0)	
Lung [N (%)]	376 (47)	315 (49)	46 (39)	11 (39)	4 (31)	
Melanoma [N (%)]	158 (20)	110 (17)	35 (30)	8 (28)	5 (39)	
Renal [N (%)]	59 (7)	52 (8)	4 (3)	1 (4)	2 (15)	
Systemic disease status						
Not Controlled [N (%)]	573 (72)	438 (68)	99 (85)	23 (82)	13 (100)	<0.001[d]
Controlled [N (%)]	228 (28)	205 (32)	18 (15)	5 (18)	0 (0)	
Karnofsky performance status (KPS)						
Mean (SD)	80 (12)	80 (12)	81 (10)	81 (10)	80 (10)	0.86[c]
KPS ≥70 [N (%)]	716 (89)	569 (88)	109 (93)	26 (93)	12 (92)	
KPS <70 [N (%)]	85 (11)	74 (12)	8 (7)	2 (7)	1 (8)	
Cumulative tumor volume						
Median (IQR)	4 (1–8)	4 (1–9)	2 (1–6)	2 (1–5)	1 (<1–2)	<0.001[a]
Cumulative tumor volume >4 cc [N (%)]	380 (47)	324 (50)	43 (37)	10 (36)	3 (23)	
Cumulative tumor volume ≤4 cc [N (%)]	421 (53)	319 (50)	74 (63)	18 (64)	10 (77)	
Number of cerebral metastases						
Median (IQR)	2 (1–5)	2 (1–4)	2 (1–6)	2 (2–7)	4 (2–5)	0.02[a]
≥3 cerebral metastases [N (%)]	334 (42)	261 (41)	53 (45)	13 (46)	7 (54)	
<3 cerebral metastases [N (%)]	467 (58)	382 (59)	64 (55)	15 (54)	6 (46)	
Whole brain radiation therapy (WBRT)						
Received WBRT [N (%)]	268 (33)	213 (33)	41 (35)	12 (43)	2 (15)	0.36[d]
No WBRT [N (%)]	533 (67)	430 (67)	76 (65)	16 (57)	11 (85)	

IQR interquartile range, *SD* standard deviation

[a] p value for independent samples Kruskal–Wallis test

[b] p value for Log Rank (Mantel Cox) test

[c] p value for one-way ANOVA

[d] p value for Pearson's χ^2 test

$\alpha = 0.05$, 95 % CI for all tests

histology (Table 2). The analysis revealed that additional SRSs did not significantly influence overall survival.

Validation of survival patterns using an independent patient cohort

To validate our findings, we performed the same statistical analysis of survival patterns using a cohort of 2472 cerebral metastases patients treated with SRS at the KHMGH. Patient characteristics for the KHMGH cohort are summarized in Online Resource 1. 3640 SRS sessions were performed for 26,629 metastases in 2472 patients with breast (n = 309, 13 %), colorectal (n = 207, 8 %), lung (n = 1840, 74 %), melanoma (n = 1, <1 %) and renal (n = 115, 5 %) cancer. The mean age of the study population was 65 (SD = 11) and mean KPS was 85 (SD = 14). The median number of cerebral metastases was 4 (range 2–10). The median cumulative tumor volume was

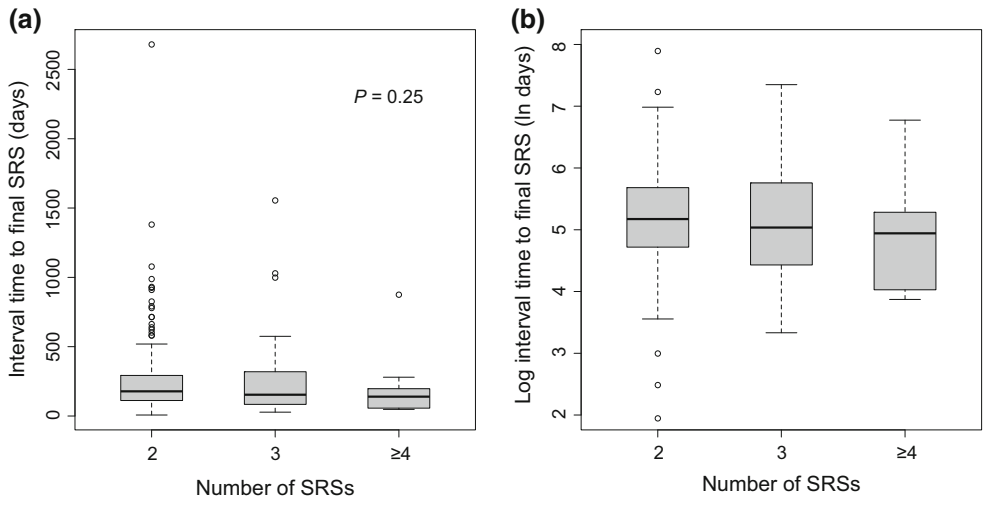


Fig. 1 Box-plots for interval (**a**) and log-interval (**b**) days to final stereotactic radiosurgery (SRS) for UCSD/SDGKC patients with brain metastases by number of SRSs

5 cc (range 1–11). Systemic control of primary disease was not achieved in the majority of the patients in this cohort (83 %). Most patients did not undergo WBRT (91 %) at any point of their clinical course. Except for paucity of melanoma in the Japanese population [20], the demographic of the multiple SRS patients were similar to the UCSD/SDGKC dataset. The KHMGH patients who underwent multiple SRSs were more likely to: (1) be age <65 ($p < 0.001$); (2) have systemic disease control ($p < 0.001$); (3) suffer from metastases with smaller cumulative tumor volume ($p < 0.001$) and, (4) have a greater number of brain metastases ($p < 0.001$).

The analysis confirmed that there was no difference in interval times to final SRS ($p = 0.31$, shown in Online Resource 2) or median survivals after the final SRS ($p = 0.73$, shown in Fig. 3). The median interval times to final SRS were 195 (range 129–329), 198 (range 131–284), and 173 (range 112–292) days for patients treated with 2, 3, and ≥4 SRS(s), respectively ($p = 0.31$). The median survival for patients undergoing 1, 2, 3, and ≥4 SRS(s) were 158 (95 % CI 149–168), 156 (95 % CI 138–168), 148 (95 % CI 131–194), and 142 (95 % CI 107–208) days, respectively ($p = 0.73$).

Discussion

While multiple sequential SRSs are routinely performed for the treatment of patients afflicted with cerebral metastases [3], the survival patterns for patients treated in this manner remain poorly studied [9]. To address this issue, we used a two-phase study design where results in one cohort were validated using a second independent cohort. The results observed in these two independent cohorts, summing to over 4500 patients with over 30,000 metastases, were remarkably consistent. In both cohorts, the median time between SRSs was approximately 5–6 months, irrespective of number of SRSs performed; most importantly, the median overall survivals of patients undergoing 1, 2, 3, or ≥4 SRS(s) were 5–6 months and did not differ significantly. Additionally, multivariate analysis incorporating age, KPS, systemic disease status, cumulative tumor volume, and primary tumor histology [19], up to four SRSs was not prognostic for worsened overall patient survival in selected patients. To our knowledge, this is the first reported documentation of these findings.

With increasing emphasis on triage of resources in health care [8], there is a trend for insurers impose "rules" for patient selection with regard to SRS [12, 21], particularly in the context of costs associated with serial SRSs [22, 23]. These rules are sometimes grounded in perception rather than rigorous analysis of clinical data. Take the number of cerebral metastasis, for instance. Proposed treatments of patients with 5–10 metastases with SRS are often scrutinized and debated. These debates persist despite a landmark prospective multicenter cohort study demonstrating that the overall survival of SRS-treated patients with 2–4 cerebral metastases was non-inferior to those with 5–10 cerebral metastases [24]. In this context, we hope that our results dispel the notion that serial development of multiple metastatic lesions in the cerebrum itself constitutes an absolute indication of poor survival. As such, the decision of SRS versus WBRT should be individually tailored, with judicious consideration of the patient's overall survival [15, 18, 19], systemic and intracranial tumor burden [11, 13, 19, 25], functional and cognitive

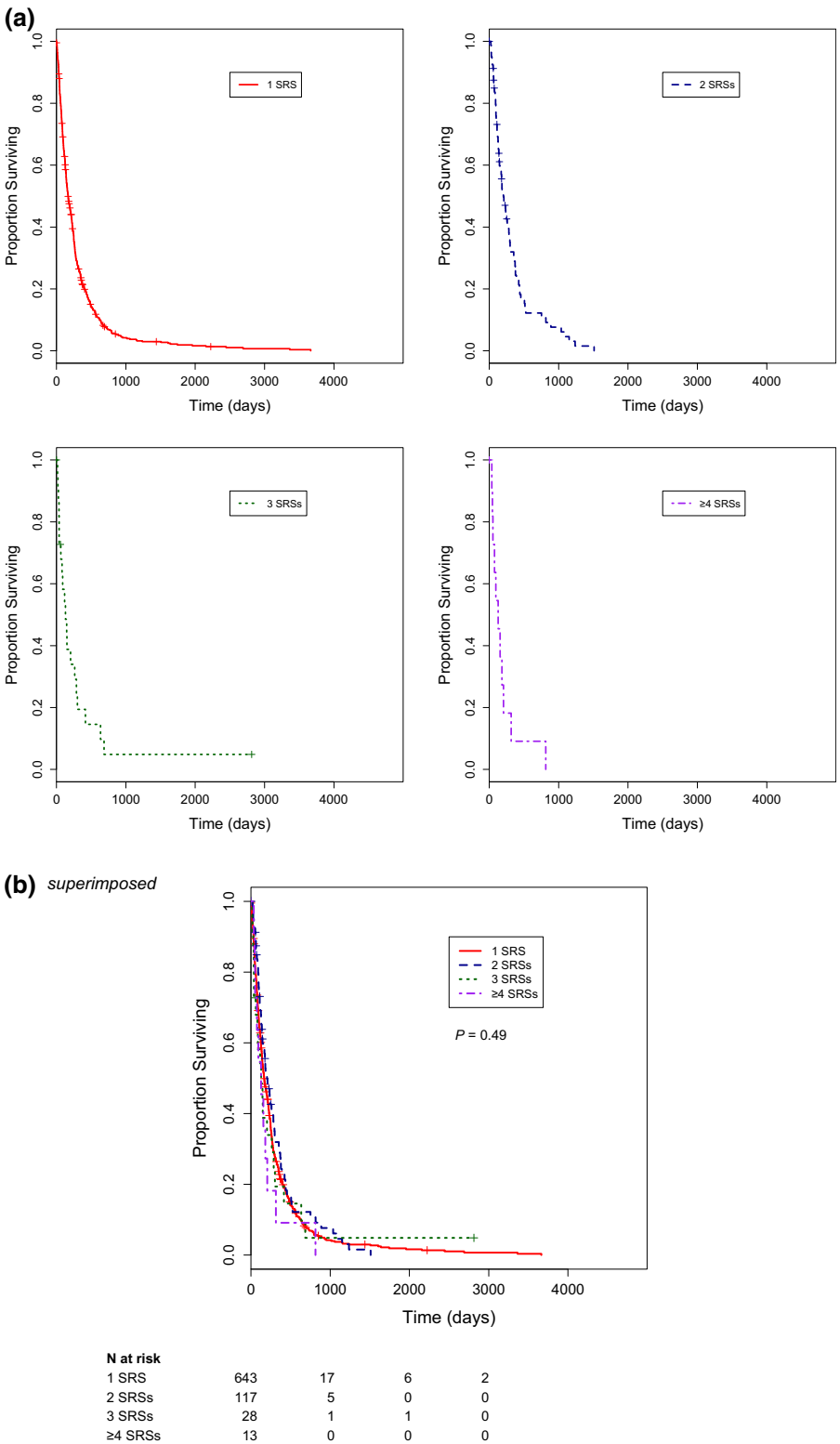


Fig. 2 Kaplan–Meier curves for overall survival of UCSD/SDGKC patients with brain metastases after final stereotactic radiosurgery (SRS) by number of SRSs (**a**) and superimposed (**b**)

Table 2 Multivariable analyses of overall survival of UCSD/SDGKC patients with brain metastases after final stereotactic radiosurgery (SRS) by number of SRSs

Covariable	Adjusted HR	95 % CI	p value[a]
Number of SRSs			
1	(1.00)		
2	0.88	0.68–1.14	0.33
3	1.32	0.84–2.08	0.23
≥4	1.22	0.66–2.26	0.52
Age ≥65		1.01–1.43	0.04
KPS ≥70	0.56	0.43–0.73	<0.001
Systemic disease control	0.50	0.41–0.61	<0.001
Number of metastases (≥3)	1.54	1.30–1.83	<0.001
Cumulative tumor volume (>4 cc)	1.26	1.06–1.49	0.007
Primary tumor histology			
Breast	(1.00)		
Lung	1.07	0.86–1.33	0.57
Melanoma	1.40	1.08–1.80	0.01
Renal	1.12	0.78–1.60	0.52
Colorectal	1.35	0.89–2.06	0.16

HR hazard ratio, *CI* confidence interval, *KPS* Karnofsky performance status

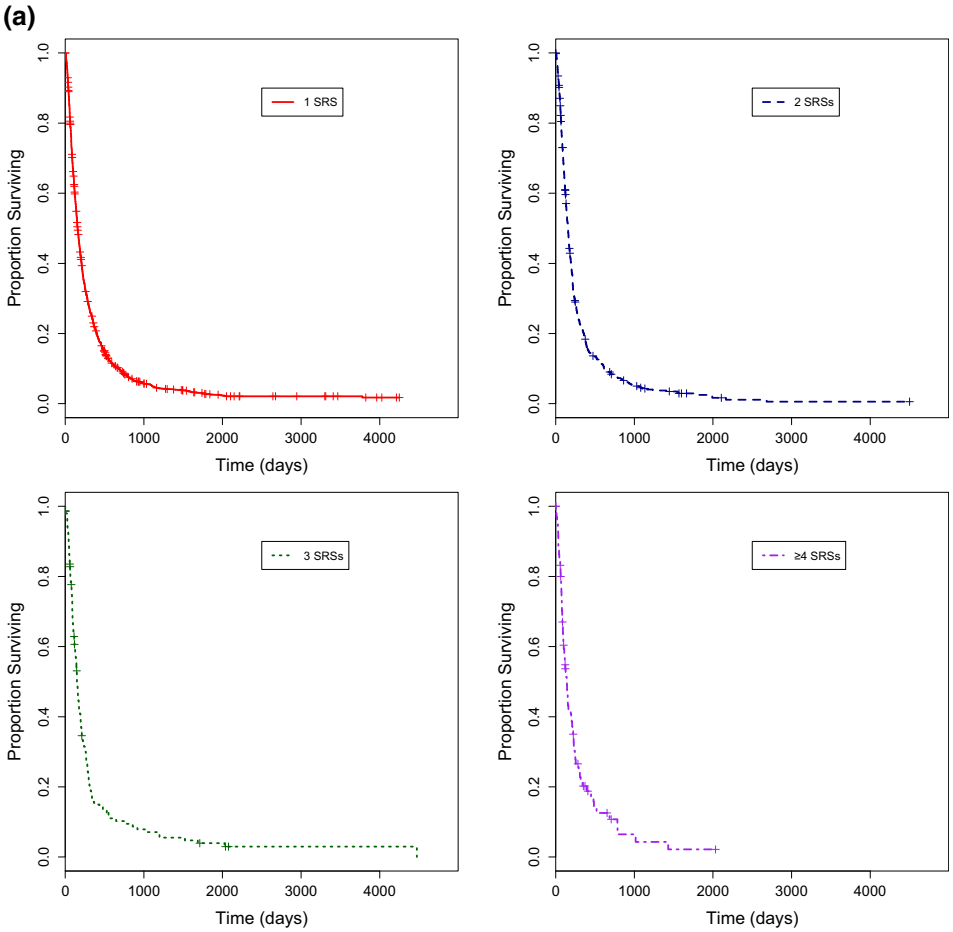
[a] Using Cox proportional hazards models, Wald test $Z = 131$, $p < 0.001$

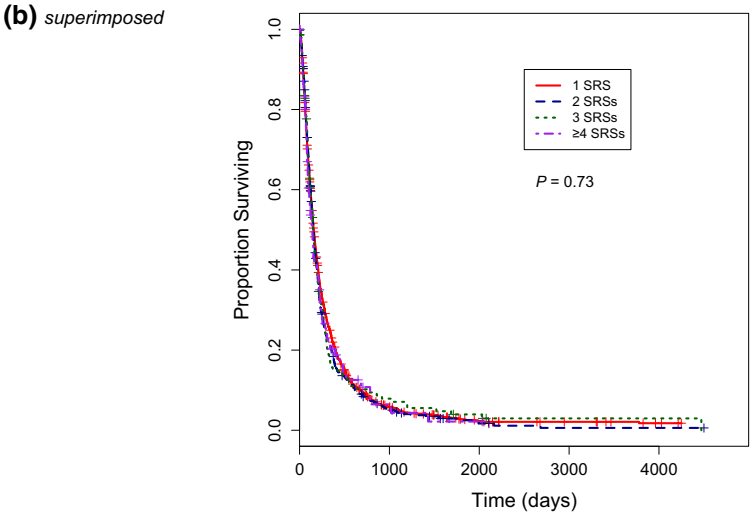
status [26–29], reliability for follow-up [30], and risk of distant metastases [31, 32]. Given that our cohort consisted of patients who were carefully selected by experienced clinicians, cautioned interpretation of the presented data is warranted. Undoubtedly, the observed survival pattern is influenced by patient selection bias since patients who underwent repeated SRS tend to be younger, with systemic disease control and with smaller cumulative tumor volume. These differences in patient demographics likely reflect criteria used for selection to undergo multiple SRSs. As such, the data should not be interpreted to mean that all patients who suffer serial development of metastases should be treated with SRS. Instead, the data argues that in carefully and judiciously selected patients, the same overall survival benefit can be achieved independent of the number of previous SRSs. Despite the findings that patients who underwent multiple SRSs tend to harbor more favorable prognostic factors (e.g. younger age and smaller cumulative tumor volume), the comparable survival between patients undergoing single versus multiple SRS(s) suggests complex biologic interaction between systemic disease progression and intracranial metastasis as determinants of overall survival.

There are several limitations inherent to our study. First, this is a retrospective experience of carefully selected patients, and as such is subject all biases inherent within such a study design. For instance, the selection of chemotherapy and radiation regimen (SRS v WBRT) likely differ between UCSD and KHMGH. Nevertheless, the consistency of the results observed in these cohorts suggest that our findings are robust despite these considerations. In support of our conclusions, comparison of our patient population to previously published SRS series [33, 34] suggests that our study population is comparable to those reported by others. For example, the distribution of our patients undergoing repeated SRS (15 % 2 SRSs, 3 % 3 SRSs, and 2 % ≥4 SRSs) is very similar to the cohort reported by Karlsson et al. [33] where 16 % underwent two SRSs, 4 % underwent 3 SRSs, and 2 % underwent ≥4 SRSs for the treatment of cerebral metastases. The duration between SRSs reported here (median of 160 days) is also comparable to that reported by Chen et al. [34], who reported a 32 week (156 days) duration between SRS treatment and disease recurrence. Ultimately, the strength of our study lies in the validation of results derived from two independent study populations with over 3000 individual patients afflicted with brain metastases derived from breast, lung, renal, and colorectal cancer. The lack of a validation melanoma cohort from KHMGH represents another limitation in our study, since melanoma has been shown to have an unrelenting course of re-seeding the brain [31, 32, 35]. As such, over-interpretation of this subset of our data should be avoided.

Conclusions

Using an independent validation study design, we demonstrated comparable overall survival between judiciously selected patients who underwent single or up to four





N at risk					
1 SRS	1697	78	20	10	3
2 SRSs	529	23	4	1	1
3 SRSs	146	10	4	1	1
≥4 SRSs	100	3	1	0	0

Fig. 3 Kaplan–Meier curves for overall survival of KHMGH patients with brain metastases after final stereotactic radiosurgery (SRS) by number of SRSs (**a**) and superimposed (**b**)

SRS(s). The decision of WBRT versus multiple SRSs should be tailored to the clinical condition of patient based on judgment of the treating physician.

Acknowledgments This study was funded in part by the National Institutes of Health (TL1TR00098 to D.C.M.; KL2TR00099 to J.H.G.; and, UL1TR000100 to J.H.G.).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study formal consent is not required. The study protocol was approved by the Institutional Review Board.

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