Prognostic Factors for stereotactic radiosurgery-treated patients with cerebral metastasis: Implications on randomised control trial design and inter-institutional collaboration

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Abstract **Introduction:** Defining key prognostic factors for patients with cerebral metastases who underwent stereotactic radiosurgery (SRS) treatment will greatly facilitate future clinical trial designs.
Methods: We adopted a two-phase study design where results from one cohort were validated in a second independent cohort. The exploratory analysis reviewed the survival outcomes of 1017 consecutive patients (with 3610 metastases) who underwent Gamma radiosurgery at the University of California, San Diego (UCSD)/San Diego Gamma Knife Center (SDGKC). Multivariate analysis was performed to identify prognostic factors. Results were validated using data derived from 2519 consecutive patients (with 17,498 metastases) treated with SRS at the Katsuta Hospital.
Results: For the SDGKC cohort, the median overall survival of patients following SRS was 7 months. Two year follow-up data were available for 85% of the patients. Multivariate analysis found that patient age, Karnofsky Performance Status, systemic cancer status, tumour

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histology, number of metastasis and cumulative tumour volume independently associated with overall survival ($p < 0.001$). All statistical associations were validated by multivariate analysis of data derived from the Katsuta Hospital cohort.

Conclusions: This is the first integrated study that defined prognostic factors for SRS-treated patients with cerebral metastases using an inter-institutional validation study design. The work establishes a model for collaborative interactions between large volume centers and provides prognostic variables that should be incorporated into future clinical trial design.

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1. Introduction

Management of patients with cerebral metastases remains a major challenge in neuro-oncology. Metastatic tumours to the cerebrum constitute one of the most common oncologic conditions of the adult central nervous system [1,2]. Though the exact incidence of cerebral metastases remains unknown, estimates suggest that up to 10% of all cancer patients will develop cerebral metastases during their clinical course [3]. Moreover, the incidence of cerebral metastases is projected to increase in the upcoming years [4]. Thus, addressing management issues related to cerebral metastases is of critical importance.

Radiation has widely been accepted as a primary modality of treatment for cerebral metastases [5]. Randomised controlled trials (RCT) have shown that whole brain radiation therapy (WBRT) increases the median survival in patients afflicted with cerebral metastasis by 3–6 months [6,7]. This therapeutic effect is unmatched by the other adjunctive modalities, including surgery [8]. The development of stereotactic radiosurgery (SRS) as a platform for radiation delivery has raised the controversy as to whether WBRT is necessary [9]. The controversy involves whether patients with limited number of brain metastasis should undergo WBRT or focal radiation (SRS) delivered only to the radiographically visible tumours.

The resolution of this fundamental question will require thoughtful clinical trials with randomised design. A major challenge in the design of such trials is that cerebral metastasis is an umbrella term that captures a highly heterogeneous population of patients with differing underlying patho-physiologies [10]. In order to advance treatment paradigms for patients with cerebral metastasis, efforts must be made to identify more homogenous disease populations. We propose that this goal can be achieved by identifying prognostic variables that proxy the underlying patho-physiologies, selecting the patient populations pertinent to the question at hand and randomising only these subsets of patients [11].

A number of prognostic factors have been proposed for patients suffering from cerebral metastases, including age [12,13], Karnofsky Performance Status (KPS) [13,14], systemic cancer status [14,15], tumour histology [16], number of metastasis [17,18] and cumulative tumour volume [19]. However, there are conflicting results in

the relative importance of these variables [20]. For instance, in the initial landmark work that defined the prognostic importance of age, KPS and systemic cancer status [13], primary tumour site did not appear to correlate with overall survival. Yet, there are a number of other studies [18,21–23] documenting that breast cancer patients with cerebral metastases exhibit improved survival. Similarly, there are significant discrepant results pertaining to the importance of cumulative tumour volume relative to the total number of metastases [18,19,24–29]. In order to move the field forward and to afford opportunities for intelligent clinical trial design, there is a critical need to perform an integrated analysis of the various proposed prognostic factors.

To this end, we retrospectively analysed our data set of 1017 consecutive patients who underwent radiosurgery for 3610 cerebral metastasis. We found independent prognostic value in all previously reported variables, include patient age, Karnofsky Performance Status, systemic disease status, tumour histology, the number of cerebral metastases and the cumulative volume of cerebral metastases. We validated our findings using another cohort of 2519 patients who underwent radiosurgery for 17,498 cerebral metastasis at the Katsuta Hospital. Future randomised trials should incorporate these variables in terms of study design.

2. Methods

2.1. Patient selection

For the initial exploratory analysis, we performed an Institutional Board Review (IRB) approved retrospective review of consecutive gamma knife SRS-treated patients for indication of cerebral metastases. The review period spanned 1994 to 2011. 1017 patients with the five most common types of cerebral metastasis (breast, lung, colon, melanoma and renal) were included in this analysis. Each patient had been referred for radiosurgery by a neurosurgeon or radiation oncologist. Data collected from the in-house electronic medical record system included age, gender, KPS, primary tumour pathology, number of metastases, volume of each tumour, history of prior radiation treatment and the last date of follow-up. We accessed the Social Security Administration Master Death Files [30] to obtain dates of all patient deaths. The validation dataset was

derived from 2519 consecutive patients who underwent radiosurgery for cerebral metastasis at the Katsuta Hospital. Details of these two patient cohorts are shown in Tables 1A and 1B [31].

2.2. Radiosurgery technique

For the San Diego Gamma Knife Center (SDGKC) patients, all radiosurgery candidates were reviewed in a multidisciplinary conference prior to assignment to SRS. SRS was performed after informed consent. Magnetic Resonance Imaging (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. Treatment plans are then formulated by the radiosurgery team consisting of a neurosurgeon, medical physicist and radiation oncologist. The Leksell Unit model B was used before 2004 and the Unit model C (Elektra Instruments, Inc) was used thereafter. Dosimetric planning was performed with Elektra'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 [32]. Additional parameters such as total number of metastases, tumour 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 validation cohort were described in a previous manuscript [31] and are highly analogous to methods described above.

2.3. Statistics

Overall survival times were estimated using the Kaplan–Meier method and compared using the log-rank test. Exploratory univariate Cox proportional hazards modelling were performed to assess the prognostic value of different variables related to overall survival. The variables analysed include: age (<65, $\geqslant 65$), KPS (<70, $\geqslant 70$), primary tumour type (breast, lung, melanoma, renal and colon) and systemic disease status (active versus non-active). The age and KPS cut-off's were imposed based on the well-established Recursive Partitioning Assessment (RPA) classification [13]. To avoid imposing any arbitrary cut-offs for continuous variables, such as the number of cerebral metastases and cumulative tumour volume, we performed the same Cox

proportional hazards modelling with different thresholds (1, 2, 3, 4... etc.) of the cumulative tumour volume and as a continuous variable. The same analysis was done for the number of metastases, as a continuous variable and dichotomised at (1, 2, 3, 4... etc.). Multivariate Cox proportional hazard modelling was then performed using age, KPS, number of cerebral metastases, cumulative tumour volume as continuous variables; systemic disease status and primary cancer histology was treated as categorical variables in this model. The correlation of cumulative tumour volume to number of metastases was further assessed by the Spearman's correlation coefficient. All statistical tests were two-tailed and a p-value < 0.05 was considered significant. All statistical calculations were performed using R programming (version 2.14.1) [33] and the survival package [34].

3. Results

3.1. Patient characteristics

Demographic information for the SDGKC cohort can be found in Table 1A. Between 1994 and 2011, 1017 stereotactic radiosurgery sessions were performed for 3610 metastases originating from breast (223), lung (457), melanoma (227), renal (71) and colorectal cancer (39). The age ranged from 22 to 92, with a median age of 58. There were approximately equal numbers of male and female patients in this cohort. There were 394 (38.7%) gamma knife procedures performed for a solitary metastasis. In patients undergoing treatment for multiple metastases, the average number of lesions was 5 (range 2–44). The total tumour volumes treated varied from 0.02 to 54.5 cm^3 (median 2.3 cm^3, mean 4.7 cm^3). The overall median survival of our patient cohort was 7 months, with 46.6%, 24.1%, 15.4% and 9.3% of patients surviving 6, 12, 18 and 24 months, respectively. Two year follow-up data were available for 785 (77.2%) of the procedures.

Demographic information for the Katsuta Hospital cohort is found in Table 1B. Between 1998 and 2013, 2519 stereotactic radiosurgery sessions were performed for 17,498 metastases originating from breast (273), lung (1638), renal (102), gastrointestinal tract (296) and other tumour types (210). The ages ranged from 19 to 96, with a median age of 65. There were 1532 male and 987 female patients in this cohort. There were 729 gamma knife procedures performed for a solitary metastasis. In patients undergoing treatment for multiple metastases, the average number of lesions was 9 (range 2–89). The total tumour volumes treated varied from 0.01 to 126.2 cm^3 (median 5.7 cm^3, mean 10 cm^3). The overall median survival of this patient cohort was 7.4 months, with 57.5%, 33.6%, 21.2% and 15% of patients surviving 6, 12, 18 and 24 months, respectively. Two year

Table 1A
Demographics for patients undergoing stereotactic radiosurgery at San Diego Gamma Knife Center.

Demographics	
Stereotactic radiosurgery (SRS) procedures	1017
Total number of tumours	3606
Primary tumour type	
Breast	223 (21.9%)
Melanoma	227 (22.3%)
Renal	71 (6.9%)
Lung	457 (44.9%)
Colorectal	39 (3.8%)
Systemic disease control	
Yes	255 (25%)
No	762 (75%)
Whole brain radiation therapy (WBRT)	
Yes	344 (33.8%)
No	673 (66.1%)
Age	
<65	342 (33.6%)
⩾65	675 (66.3%)
KPS	
<70	928 (91.2%)
⩾70	89 (8.7%)
Volume	
⩽4 cc	557 (54.8%)
>4 cc	460 (45.2%)
Number of metastasis	
1–2	595 (58.5%)
3+	422 (41.4%)

Table 1B
Demographics for patients undergoing stereotactic radiosurgery at the Katsuta Hospital.

Demographics	
Stereotactic radiosurgery (SRS) procedures	2519
Total number of tumours	17,498
Primary tumour type	
Lung	1638 (65%)
Gastrointestinal tract	296 (11.8%)
Breast	273 (10.8%)
Renal	102 (4%)
Other	210 (8.3%)
Systemic disease control	
Yes	723 (28.7%)
No	1796 (71.3%)
Whole brain radiation therapy (WBRT)	
Yes	120 (4.8%)
No	2399 (95.2%)
Age	
<65	1332 (52.9%)
⩾65	1187 (47.1%)
KPS	
<70	2348 (93.2%)
⩾70	171 (6.8%)
Volume	
⩽4 cc	1012 (40.2%)
>4 cc	1507 (59.8%)
Number of metastasis	
1–2	1110 (44.1%)
3+	1409 (55.9%)

follow-up data were available for 2510 (99.6%) of the procedures.

3.2. Dosimetric parameters

The median radiation dose delivered to the tumour margin was 19 Gy (mean 18.9 Gy, range 9–28 Gy). The prescribed radiation doses correlated inversely with cumulative tumour volumes (rho = -0.385, $p < 0.001$). (Fig. 1A) Patients who underwent WBRT (33.8%) prior to SRS received lowered SRS dose (mean 18.5 versus 19.1 Gy, $p = 0.003$) relative to those who underwent upfront SRS. There was no significant correlation between prescribed radiation dose with tumour number (rho = -0.01, $p = 0.537$, Fig. 1B) or other clinical variables. For the validation cohort, the median radiation dose delivered to the tumour margin was 21.1 Gy (range 10–32 Gy). As with the SDGKC dataset, the prescribed radiation doses in the Katsuta Hospital dataset correlated inversely with cumulative tumour volumes (rho = -0.179, $p < 0.001$).

3.3. Survival by patient characteristics: age, KPS and systemic disease control

Univariate analysis using RTOG established cut-offs for age, KPS and systemic disease control confirmed the statistical association between these variables and the overall survival of patients with cerebral metastases (Fig. 2A–C). When grouped by RTOG Recursive Partitioning Analysis (RPA) classification [13], the median survivals were: 9 months for RPA class I ($n = 494$), 5 months for RPA class II ($n = 434$) and 3 months for RPA class III ($n = 89$) (Fig. 2D). The differences in the overall survival of these groups were statistically significant ($p < 0.001$).

3.4. Survival analysis by Graded Prognostic Assessment

When grouped by the Graded Prognostic Assessment (GPA) classification based on the scale defined by Sperduto et al. [12], the median survivals were: 11 months for GPA score 3.5–4 ($n = 147$), 9.7 months for GPA score 3 ($n = 214$), 6.2 months for GPA scores 1.5–2.5 ($n = 540$) and 2 months for GPA scores 0–1 ($n = 116$). The difference in the overall survival of these groups was statistically significant ($p < 0.001$) (Fig. 3A).

3.5. Tumour histology and prior WBRT

By univariate analysis, the overall survival of our patients differed significantly depending on the histology of the cancer type ($p = 0.01$, Fig. 3B). Breast cancer patients had the longest median survival (9 months)
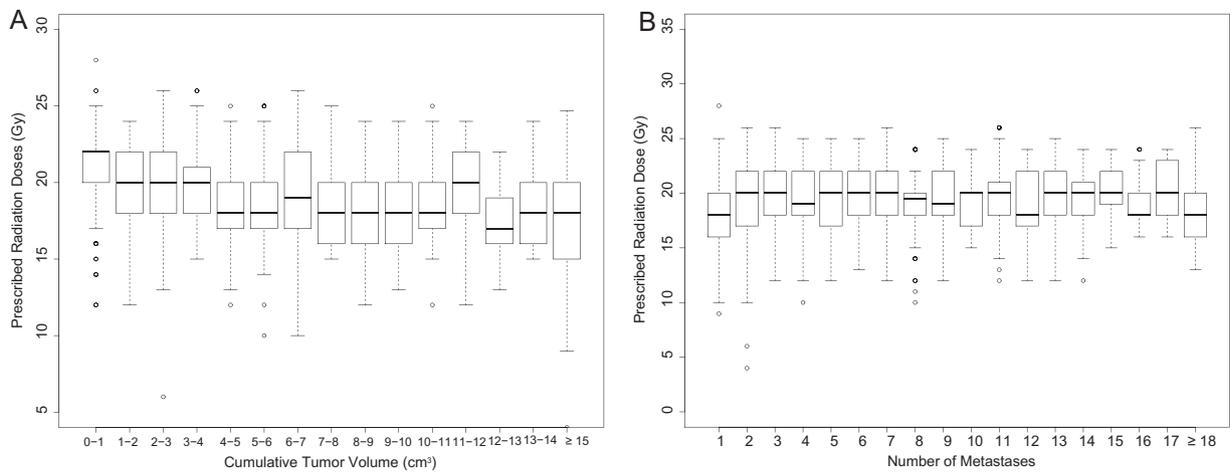
Fig. 1. Box plots comparing the radiation doses (Gy) prescribed to patients by their respective cumulative tumour volume (A), and number of metastases (B).
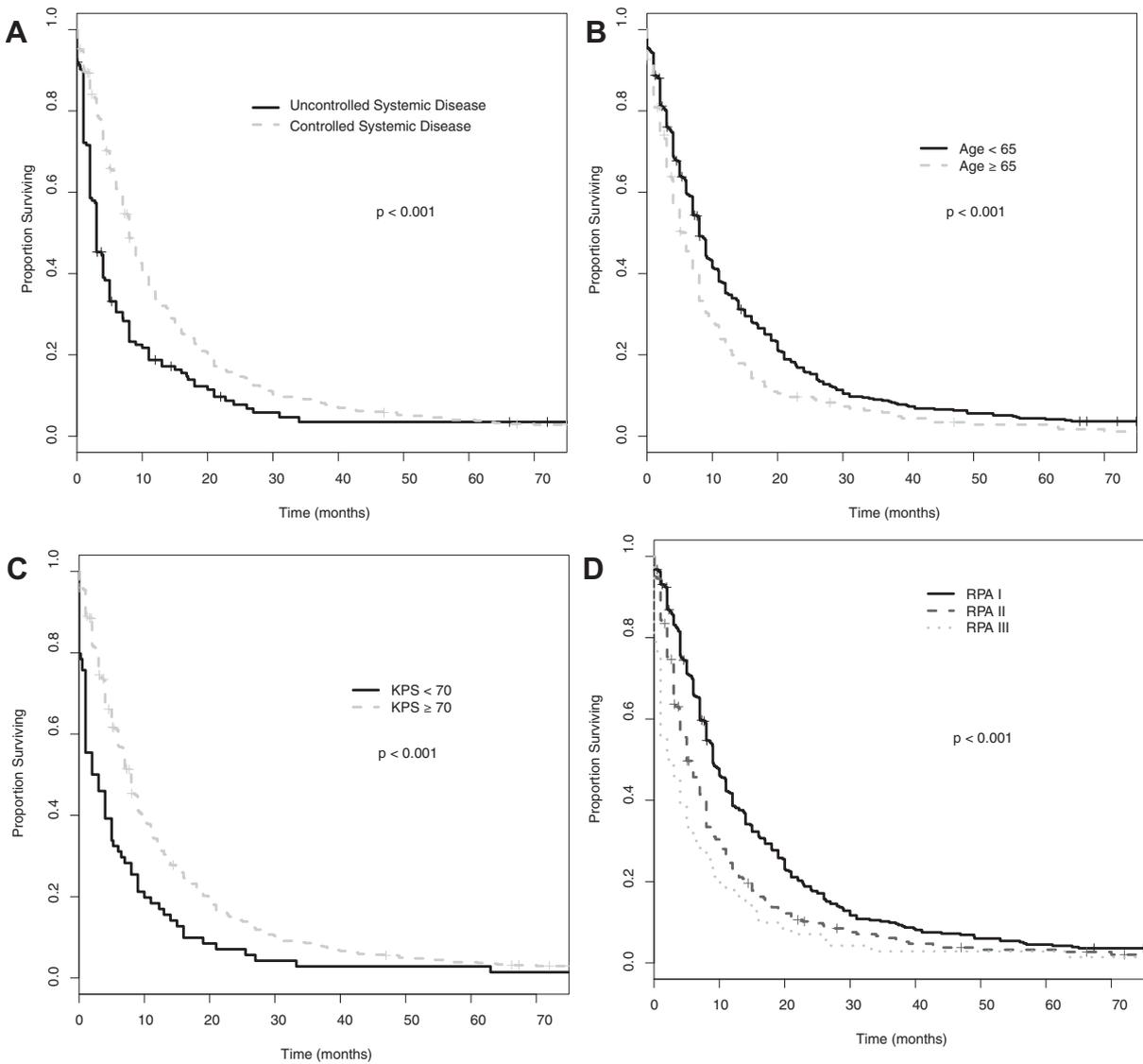

Fig. 2. Kaplan Meier curves for overall survival after stereotactic radiosurgery (SRS) by (A) Radiation Therapy Oncology Group (RTOG)-Recursive Partitioning Assessment (RPA) class, (B) age (<65 year-olds), (C) KPS (<70) and (D) systemic disease control. All were statistically significant by log rank sum with *p*-values < 0.001.
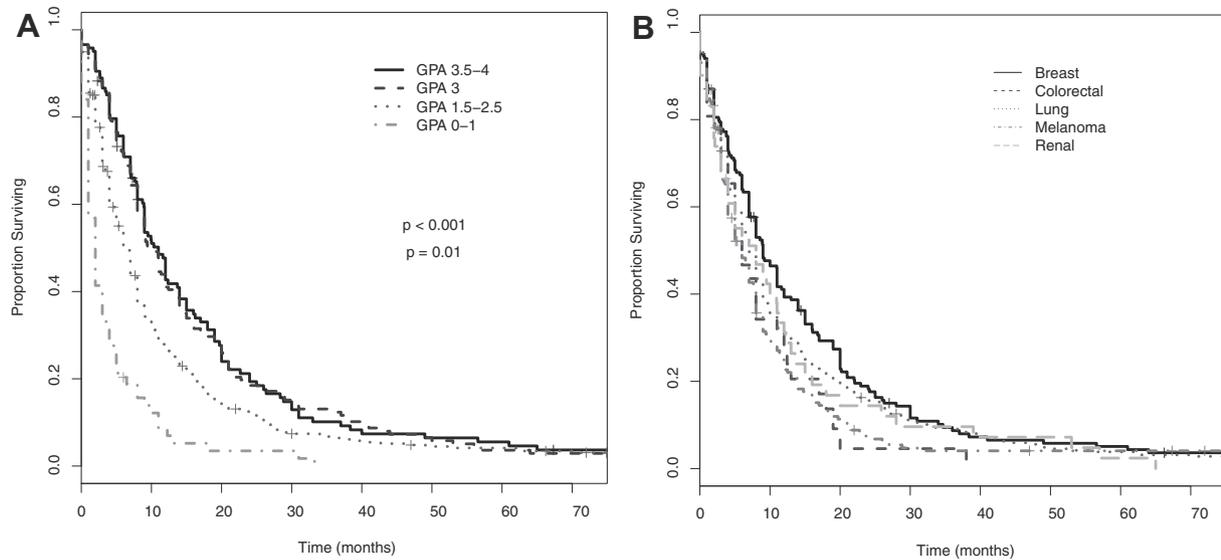
Fig. 3. Kaplan Meier curves for overall survival after stereotactic radiosurgery (SRS) by (A) Graded Prognostic Assessment (GPA) index scores and (B) primary tumour type (melanoma and breast, colorectal, lung and renal carcinomas).

while melanoma and colorectal carcinoma patients had the lowest median survivals (6 months). On the other hand, the overall survival of patients who underwent WBRT prior to SRS did not significantly differ from those who underwent upfront SRS ($p = 0.889$).

3.6. Survival by metastases number and cumulative tumour volume

When analysed as a sliding dichotomised variable, number of metastases was significant when divided at 1, 2, 3, or 4 metastases but not for >5 metastases (Table 2). Importantly, there is a graded decrease in

Table 2
Univariate and multivariate analyses[¥] of patient survival using differing thresholds of metastases number and cumulative tumour volume[*].

	Univariate		Multivariate	
	HR	p-Value	HR	p-Value
Number of metastases				
>1	1.146	0.0653	1.129	0.1141
>2	1.392	<0.0001	1.366	<0.0001
>3	1.326	0.0003	1.269	0.0035
>4	1.29	0.0026	1.225	0.0204
>5	1.156	0.1272	1.064	0.5258
Continuous	1.025	0.0021	1.01	0.2144
Cumulative tumour volume (cc)				
>1	1.359	0.0003	1.287	0.0039
>2	1.366	<0.0001	1.292	0.0009
>3	1.473	<0.0001	1.467	<0.0001
>5	1.544	<0.0001	1.494	<0.0001
>10	1.759	<0.0001	1.602	<0.0001
Continuous	1.034	<0.0001	1.031	<0.0001

[¥] Using Cox proportional hazard model.
[*] Variables used for multivariate analysis are the same as in Table 3 with number of metastases and tumour volume as continuous variables.

the overall survival as the number of cerebral metastasis increases – up to a total of five metastases. Similar analysis revealed a graded decrease in overall survival as the cumulative tumour volume increases (Table 2). There was little correlation between the number of metastases and cumulative tumour volumes (rho = 0.1871) (Fig. 4), suggesting these variables independently associate with overall survival. The majority of patients (54.8%) had cumulative tumour volumes less than 4 cm^3 regardless of number of metastases.

3.7. Multivariate analysis

Variables identified to associate with overall survival in the univariate analysis were then subjected to multivariate analysis, including RPA class, tumour histology, number of metastasis, cumulative tumour volume and the number of metastasis. RPA class and tumour histology were treated as categorical variables in the multivariate model. The number of metastases and cumulative tumour volume were treated as continuous variables in the model. All variables remain statistically significant in this multivariate analysis (Table 3). Importantly, survival trends in GPA 1.5–2.5 and GPA 3 patients can further be sub-divided by the cumulative tumour volume (Fig. 5). Similar results were obtained when the analysis was performed using diagnosis specific GPA [21] for the SDGKC lung cancer patients (Supplemental Fig. 1).

3.8. Validation of prognostic factors using an independent patient cohort

To validate our findings, we performed the same statistical analysis using a cohort of 2519 cerebral metastasis patients treated with SRS at the Katsuta Hospital. Demographic data for this cohort are shown
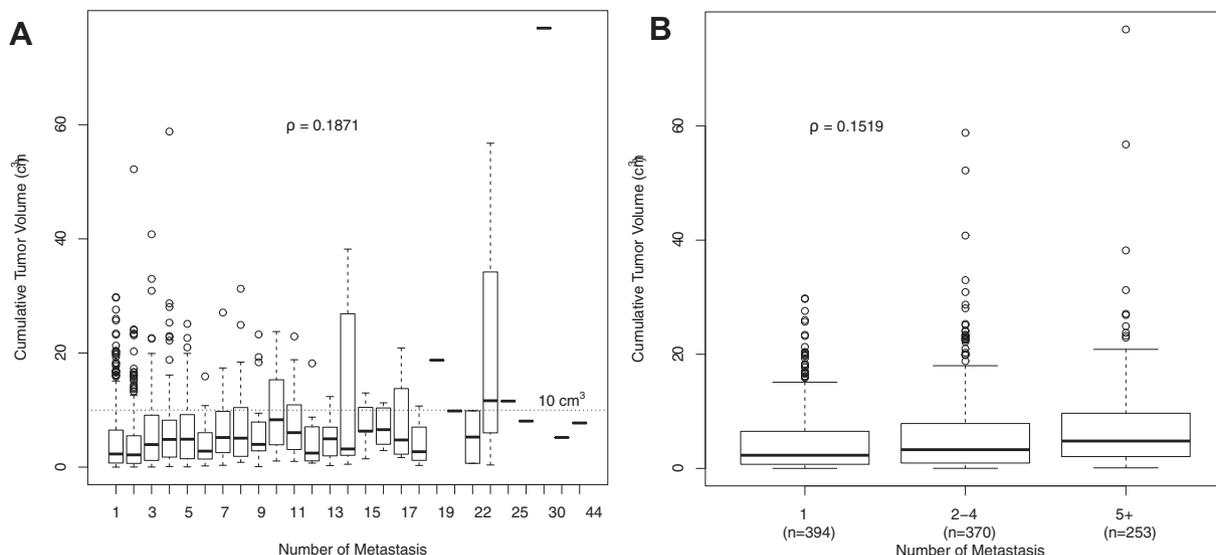
Fig. 4. Box plots (Tukey method) comparing cumulative tumour volume of patients with differing number of metastases. (A) Tumour volumes by individual number of metastases. Dotted line shows 10 cm³ volume. (B) Tumour volume by number of metastases by groups (isolated metastasis, 2–4 metastases and >4 metastases). Spearman's rank coefficient shows weak correlation between the two variables of tumour volume and number of metastases in both cases (rho = 0.1871 and 0.1598 respectively).

Table 3
Univariate and multivariate analyses of University of California, San Diego (UCSD)/San Diego Gamma Knife Center (SDGKC) cohort to identify independent prognostic factors.

Covariate	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Time period (per 6 year increase)	0.985	(0.889–1.09)	0.7677	1.033	(0.93–1.147)	0.5498
Age (65+)	1.415	(1.22–1.642)	<0.001	1.346	(1.147–1.579)	<0.001
KPS (70+)	0.543	(0.428–0.69)	<0.001	0.58	(0.452–0.744)	<0.001
Systemic disease control	0.574	(0.48–0.686)	<0.001	0.577	(0.482–0.692)	<0.001
Whole brain radiation therapy (WBRT)	0.989	(0.853–1.148)	0.8869	0.966	(0.823–1.135)	0.6748
Number of metastases (3+)	1.392	(1.204–1.608)	<0.001	1.364	(1.172–1.589)	<0.001
Tumour volume (>4 cc)	1.549	(1.341–1.79)	<0.001	1.485	(1.28–1.724)	<0.001
Primary tumour type			<0.001			<0.001
Breast	(1.00)			(1.00)		
Lung	1.168	(0.97–1.407)		1.146	(0.943–1.392)	
Melanoma	1.445	(1.166–1.79)		1.596	(1.275–1.997)	
Renal	1.272	(0.927–1.747)		1.207	(0.87–1.675)	
Colorectal	1.496	(1.018–2.199)		1.346	(0.983–2.176)	

HR = hazard ratio, CI = confidence interval.

in Table 1B. The analysis confirmed the prognostic value of RPA classification, tumour histology, cumulative tumour volume and the number of metastasis pertaining to overall patient survival (Table 4). Specifically, lower RPA class and breast cancer histology were associated with improved overall survivals. Increased cumulative tumour volume and increased number of cerebral metastasis were associated with worsened survival in a graded manner.

4. Discussion

Proper RCT design requires randomization of all pertinent prognostic variables to each treatment arm [35]. Identifying these variables will greatly facilitate the intelligent design of RCTs that optimise the statistical power of the studies. Here we report the largest study published to date that aimed to define prognostic factors associated with SRS-treated patients with cerebral metastasis using an integrative approach. The study population includes over 3000 patients and 21,000 metastases. Importantly, the study utilises a two-phase design where results from one cohort were validated using a second independent cohort. Through our analysis, we have identified age, KPS, systemic cancer status, cancer histology, number of metastases and cumulative tumour volume as mutually independent variables of prognostic value. Consistent with other reports [36], we did not find WBRT to be associated with an effect on overall survival.
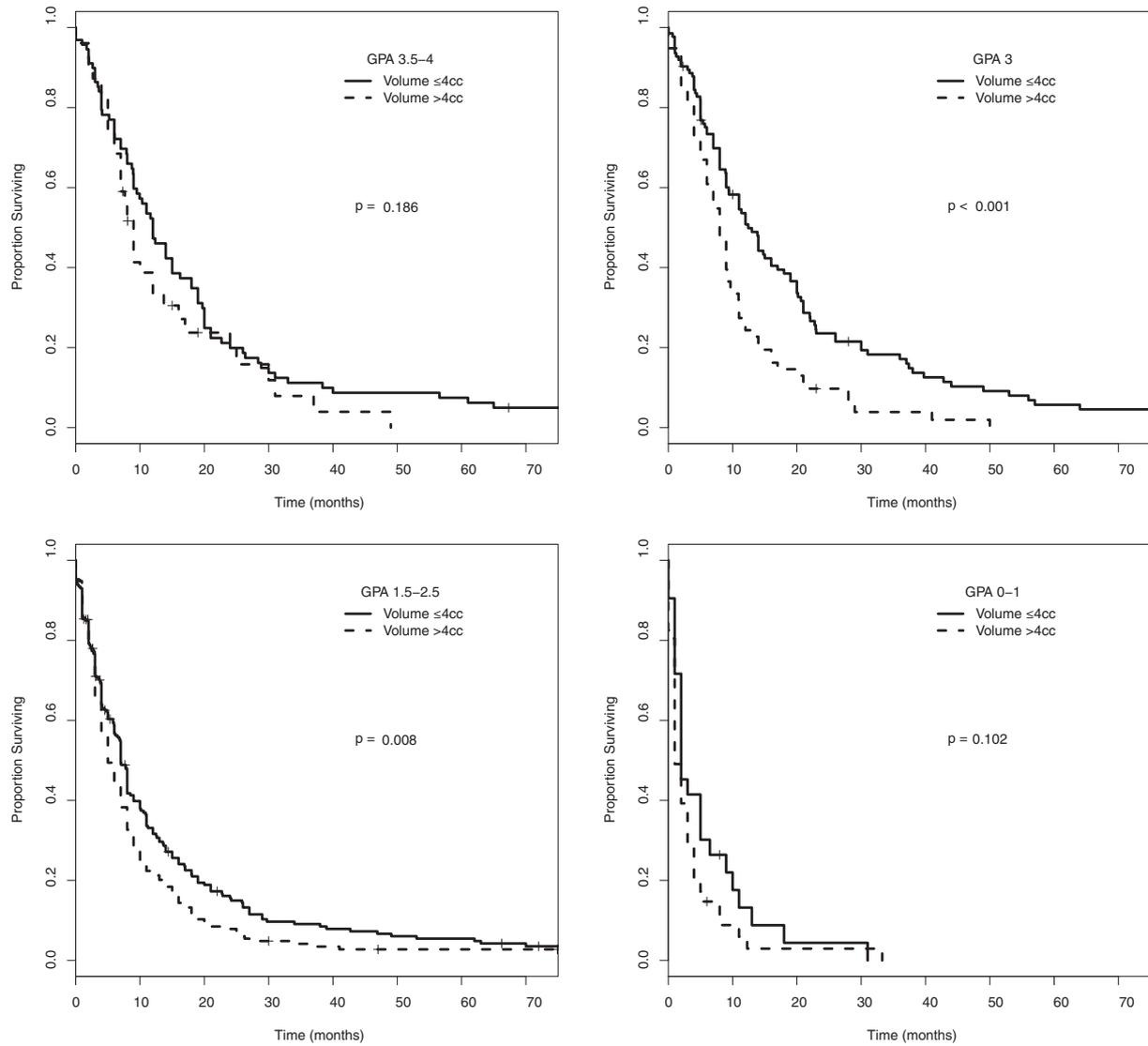
Fig. 5. Kaplan Meier curves for overall survival demonstrating the effect of volume on Graded Prognostic Assessment (GPA) categorised survivals for all tumours.

Table 4
Univariate and multivariate analyses of Katsuta Hospital cohort to identify independent prognostic factors.

Covariate	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (65+)	1.185	(1.094–1.284)	<0.001	1.161	(1.070–1.126)	<0.001
KPS (70+)	0.348	(0.297–0.407)	<0.001	0.474	(0.403–0.557)	<0.001
Systemic disease control	0.425	(0.387–0.466)	<0.001	0.449	(0.407–0.495)	<0.001
Whole brain radiation therapy (WBRT)	1.04	(0.862–1.254)	0.682	1.068	(0.884–1.289)	0.497
Number of metastases (3+)	1.471	(1.356–1.596)	<0.001	1.375	(1.265–1.495)	<0.001
Tumour volume (>4 cc)	1.429	(1.317–1.552)	<0.001	1.294	(1.189–1.409)	<0.001
Primary tumour type			<0.001			0.028
Breast	−1			−1		
Gastrointestinal	1.734	(1.465–2.052)		1.22	(1.021–1.458)	
Renal	0.989	(0.781–1.252)		0.899	(0.707–1.144)	
Lung	1.189	(1.041–1.357)		0.88	(0.763–1.016)	
Other	1.206	(1.001–1.453)		0.917	(0.757–1.110)	

HR = hazard ratio, CI = confidence interval.

Sperduto et al. reported the GPA index as a means to provide reliable prognostic information for patients with cerebral metastases [20]. The index incorporates variables of age, KPS, the presence of extra-cranial metastases and the number of cerebral metastases. In the SDGKC cohort, we found that this grading scale yielded subgroups of distinct overall survival. Importantly, stratification of GPA 1.5–2.5 and GPA 3 patients by cumulative tumour volume further defined subgroups of patients with distinct overall survival trends (Fig. 5). Similar results were observed when the data were filtered through the lens of diagnosis specific GPA (Supplemental Fig. 1). These results provide strong support to our thesis that the number of metastases and the cumulative tumour volume constitute independent prognostic factors in terms of overall survival.

The importance of age, KPS and systemic disease status as they relate to overall survival is well-documented in the literature [13]. However, the prognostic importance of tumour histology, number of metastasis and cumulative tumour volume are somewhat mixed. Some studies emphasised the statistical association of one or more of these variables to survival using arbitrary cut-offs of clinical variables that are continuous by their very nature. For instance, Likhacheva et al. published that the cumulative volume, arbitrarily defined by >2 cc or <2 cc, was associated with overall survival while the number of metastases and the tumour's histology were not. On the other hand, Petrovich et al. reported that the number of cerebral metastases (arbitrary defined by patients with 1–3 metastases versus the rest) and breast cancer as the primary histology were significant prognostic variables [23]. Still, others report findings that dispute the importance of these variables. Our study provides strong support for improved overall survival for breast cancer patients with cerebral metastases. Further, our findings suggest that the number of metastases and the cumulative tumour volume are continuous variables that independently associate with overall survival.

We propose that the differences observed here from those previously published relate to sample sizes and to the heterogeneity in disease physiology. With each new clinical variable investigated in a multivariate model, the sample size required for detecting a specific statistical association is increased. Moreover, heterogeneity disease physiology implies that larger number of patients will need to be examined in order to have sufficient representation of each disease subtype. Previous published studies were case series analysing 50–460 patients, and it is highly likely that these sample sizes offer limited views of the underlying reality. The strength of our study lies in the cross-validation of results derived from two independent study populations with over three thousands patients in total. The consistency of thesis derived from these populations render this study the most definitive study of prognostic factors for patients with cerebral metastases to date. While our study is still subject to all limitations related to a retrospective data analysis, including patient selection bias, it does emphasise the value of careful data collection and clinical follow-up on the institutional level and the importance of inter-institutional collaborative investigations as a research paradigm.

The observation that cumulative tumour volume and the number of cerebral metastases both associate with overall survival as continuous variables warrants further comment. There is a large body of literature that suggests negative consequences of arbitrarily dichotomising variables that are inherently continuous [37]. These consequences range from artifactual statistical associations to compromising the statistical power of any particular dataset [37]. Yet, this practice is rampant in the study of cerebral metastases. For instance, even seminal studies in our field impose arbitrary dichotomy in terms studying patients with single [32], 1–3 [32], 1–4 [38], or 5–10 [39], or greater than 10 [40] metastases or impose post hoc analysis based on similarly arbitrary categories. Our study demonstrated that the number of cerebral metastases and cumulative tumour volumes are continuous variables that associate with overall survival in a graded manner. Dichotomising these variables in the future studies, RCT or otherwise, must be grounded in sound biological or statistical justifications.

It is likely that the clinical variables identified here represent proxies for the heterogeneity of patho-physiologies inherent in patients with cerebral metastases. The improved prognosis of breast cancer patients with cerebral metastases likely reflects the general biology of breast cancer relative to other cancer types. The number of cerebral metastases may be a reflection of a biology that renders the cancer cells either more or less likely to undergo metastatic spread. Since metastatic spread remains the key contributor to patient lethality, it stands to reason that patients harbouring cancer cells that inherently possess limited metastatic potential will exhibit better clinical outcome. The cumulative volume may be a reflection of the proliferative potential of the metastatic cancer cell. Alternatively, since dose tolerance is inversely proportional the cumulative tumour volume, the statistical association with tumour volume may be a reflection of lowered doses delivered to the lesion(s). Studies into the biologic meaning of the various clinical variables described here should afford insights into therapeutic development or refinement of treatment protocols for patients with cerebral metastases. For instance, if the association with cumulative tumour volume is a reflection of radiation dose limitation, then surgical resection of the larger tumours followed by SRS to the smaller collapsed resection cavity may confer survival benefit to a subset of patients.

Based on our study, we would broadly propose an end to the practice of grouping cerebral metastases from breast cancer with those of other primary sites. Realising the literature demonstrating the importance of molecular subtypes in breast cancer [41], we would further suggest that studies going forward select or stratify patients based on molecular subtype. Our study also suggests that the arms of the RCT must be balanced in terms of KPS, systemic disease status, cumulative tumour volume, as well as the number of metastasis. We believe that only through such clinical trial designs can we advance the care of patients with cerebral metastases.

5. Conclusion

This study is the largest study to use a cross-institutional study design to identify prognostic variables for patients with cerebral metastases using clinical data derived from over three thousand patients. The work is also the first to present an integrative analysis of the various prognostic variables proposed by previous studies. Our analysis revealed six independent prognostic variables that should be incorporated into the design of future RCTs, including patient age, KPS, systemic disease status, tumour histology, number of metastasis and cumulative tumour volume. The work further highlights the importance of cross-institutional validation of clinical observations as a model for future investigations.

Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2014.01.001.

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