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Original Article

Radiological Kinetics of Brain Metastases and Clinical Implications for Patients Treated With Stereotactic Radiosurgery

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Abstract

Aims: Select patients with brain metastases receive stereotactic radiosurgery (SRS) with the objective of improving survival and intracranial disease control. Brain metastases number and volume are prognostic factors used to inform patient selection. The aim of this study was to assess the rate of change of brain metastases size and number (growth kinetics) between the diagnostic and day of SRS magnetic resonance imaging (MRI) scans.
Materials and Methods: All patients treated with Gamma Knife SRS between October 2015 and April 2017 were included in this single-centre retrospective analysis. Brain metastases number and diameter were recorded at diagnosis and treatment. For patients with multiple brain metastases, the largest lesion was the index lesion. Distant intracranial control and overall survival were reported from the date of SRS.
Results: In total, 146 patients received 156 episodes of SRS. The median interval between diagnostic and SRS MRI was 20 days (range 1–68). Interval growth in the index lesion of at least 3 mm or the development of a new brain metastasis was noted in 60.2% of patients. This was associated with age less than 60 years ($P = 0.001$), Eastern Cooperative Oncology Group (ECOG) performance status 2 or above ($P = 0.04$), non-small cell lung carcinoma (NSCLC) ($P = 0.03$) or melanoma histologies ($P = 0.05$) and uncontrolled extracranial disease ($P = 0.05$). These patients were also more likely to develop distant intracranial recurrence ($P = 0.046$). Clinically significant growth was not associated with scan interval or differences in overall survival. The Kaplan–Meier estimate of probability of survival at 12 months was 59.3% (95% confidence interval 46.7–75.2%) for all patients.
Conclusion: Intracranial progression between diagnosis and day of SRS is common. Risk factors are uncontrolled extracranial disease, poorer performance status, NSCLC or melanoma histologies and age less than 60 years. These patients would benefit from an MRI closer to treatment to inform patient selection and target delineation for SRS planning.

Key words: Brain metastases; Gamma Knife; radiological kinetics; stereotactic radiosurgery

Introduction

Brain metastases occur in 20–40% of all patients with advanced malignancy [1]. Prognosis varies according to primary tumour histology, performance status, age, number and volume of brain metastases and burden of extracranial disease (ECD) [2–4]. Treatment recommendations are individualised and surgery or stereotactic radiosurgery (SRS) may be considered for patients with a more favourable prognosis and whole brain radiotherapy (WBRT) or best supportive care for patients with a less favourable prognosis [1,5,6]. Poor intracranial control has been associated with an increased risk of neurological death and inferior survival [7].

SRS is a non-invasive alternative to open surgery for single brain metastases [6]. Randomised data show that both modalities improve survival compared with WBRT alone and SRS also improves functional independence and reduces steroid requirement in patients with up to three brain metastases [1,8,9]. For patients with a limited volume of intracranial disease, brain metastasis number may be a less relevant concern. Select patients with two to four brain

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metastases versus five to 10 brain metastases treated with Gamma Knife SRS have been shown to have non-inferior outcomes and toxicity [4,10].

Although brain metastases number and volume are useful factors used to inform management [3], it is unclear whether the rate of change (growth kinetics) may also have clinical relevance and utility. This study aimed to quantify brain metastasis growth kinetics and correlate with distant intracranial control in patients treated with SRS.

Materials and methods

All patients referred for SRS at our centre are discussed in a multidisciplinary team (MDT) meeting comprising radiation oncologists, neurosurgeons, a neuroradiologist and other health professionals. Patients are required to undergo contrast-enhanced magnetic resonance imaging (MRI) brain with at least 3 mm axial slice thickness within 4 weeks and appropriate extracranial restaging within 8 weeks of assessment for treatment. In general, selection criteria for SRS are $\leq$10 brain metastases with any single lesion $<$10 cm^3, total cumulative intracranial volume $<$15 cm^3, performance status Eastern Cooperative Oncology Group (ECOG) 0–2, controlled ECD and an expected prognosis of at least 6 months. Rarely, select patients with a greater number of brain metastases that have progressed after WBRT may be considered for salvage SRS. SRS planning and delivery is carried out in a single outpatient procedure using the Gamma Knife Perfexion system (Elekta Instruments, Stockholm, Sweden) with invasive headframe. On the day of treatment, a volumetric stereotactic 3T MRI brain is acquired 10 min after gadolinium contrast administration with 1.5 mm axial slice reconstruction. Gross disease is defined as the enhancing tumour and no margin is added for treatment planning purposes. Dosimetry is calculated in real time using the GammaPlan treatment planning system (Elekta Instruments). The prescribed dose is standardised according to individual brain metastasis volume, location and total brain metastases number based on an institutional adaptation of the Radiotherapy Oncology Group 95-08 protocol [11]. All patients undergo repeat MRI brain within 3 months after SRS and then surveillance imaging every 3 months for at least 2 years if clinically appropriate. All pre- and post-SRS imaging is interpreted by the same team of neuroradiologists using a picture archiving and communication system.

Following institutional ethics approval, a retrospective review was conducted of all patients with brain metastases treated with SRS between October 2015 and April 2017. Relevant clinical and demographic data were extracted from electronic medical records. The change in brain metastases number and size between diagnostic and treatment MRI was assessed. For patients with multiple brain metastases, changes in size were based on the axial diameter of the largest brain metastasis on the diagnostic MRI (index lesion). Clinically significant progression was defined as an increase in brain metastases number or growth of the index lesion by at least 3 mm in greatest axial diameter. The latter was chosen because 0–2 mm expansions are typically used for SRS in most settings [12] and therefore growth of this magnitude could lead to considerable tumour underdosing at the periphery. Patients with seizures, focal neurology or symptoms requiring corticosteroids were designated as symptomatic. In general, SRS was delivered at least 5 days from administration of cytotoxic chemotherapy, 0–3 days for targeted agents, and immunotherapy continued uninterrupted. Controlled ECD was defined as absent or stable ECD on radiology. Patients with less than 3 months of follow-up were excluded from survival analyses. Dates of last contact or death were considered as censoring times if earlier than the date of recurrence.

Descriptive statistics were reported as mean and standard deviation for normally distributed continuous data or median and interquartile range (IQR) for non-normally distributed data. Normality was assessed using a Shapiro–Wilk test. Categorical variables were presented as frequencies and percentages. Univariate analysis for potential predictors of clinically significant intracranial progression between diagnostic and SRS MRI were carried out using chi-square or Fisher's exact test for categorical variables and the Mann–Whitney test or Kruskal–Wallis test for continuous variables. All variables with a P-value < 0.2 in the univariate analysis were included in a multiple logistic regression with stepwise selection. Adjusted odds ratios and 95% confidence intervals were reported. Estimated overall survival and distant intracranial control were calculated using the Kaplan–Meier method with 95% confidence intervals. A comparison between groups was carried out using the Log-rank test. All analyses were carried out using the R statistical software [13] and P-values < 0.05 were considered statistically significant.

Results

In total, 146 patients with 524 brain metastases received 156 sessions of SRS during the study period. Baseline characteristics are given in Table 1. Eighty-one per cent of diagnostic MRIs were carried out outside our institution and the median slice thickness for these scans was 1 mm (IQR 1–1.5). The median interval between diagnostic and treatment MRI was 20 days (range 1–68; IQR 13–28.3) and 75% of the population were treated within 30 days of the diagnostic MRI. The median number of brain metastases treated per SRS session was 2 (range 1–29; IQR 1–4). The mean cumulative intracranial volume per patient was 3.44 ± 2.71 cm^3. The median SRS dose delivered was 20 Gy (range 15–24; IQR 20–22).

Change in Size of Brain Metastases

Comparing the diagnostic and SRS MRI, any change in index lesion diameter occurred in 125 patients (80%) and this was at least 3 mm in 67 patients (43% overall). The median axial diameter of the index lesion increased from 12 mm (IQR 9–16) to 15 mm (IQR 11–19) (Figure 1). Increasing brain metastasis diameter $\geq$ 3 mm between diagnostic and

Table 1
Patient demographics

***n* = 146 (total patients)**		
Gender		
Female	76 (52%)	
Male	70 (48%)	
Age (years)	60.0 (±14.2)	
ECOG		
0	51 (35%)	
1	86 (59%)	
2	9 (6%)	
3 or 4	0	
Primary histology		
NSCLC	47 (32%)	
Wildtype	74%	
EGFR/ALK mutant	26%	
Melanoma	42 (29%)	
BRAF wildtype	57%	
BRAF mutant	43%	
Breast	22 (15%)	
HER2 negative	59%	
HER2 positive	41%	
Colorectal	11 (8%)	
Renal cell carcinoma	9 (6%)	
Other	15 (10%)	
***n* = 156 (total SRS sessions)**		
Brain metastases-directed therapy before SRS		
Nil	98 (63%)	
WBRT	15 (10%)	
SRS	36 (23%)	
Surgery	7 (4%)	
Symptomatic		
Yes	63 (40%)	
No	93 (60%)	
Controlled extracranial disease		
Yes	132 (85%)	
No	24 (15%)	
Brain metastases number	Diagnostic MRI	Treatment MRI
1	65 (42%)	50 (32%)
2–3	57 (36%)	54 (35%)
4–5	23 (15%)	25 (16%)
6–10	6 (4%)	22 (14%)
>10	5 (3%)	5 (3%)

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung carcinoma; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; MRI, magnetic resonance imaging.

SRS MRI was associated with uncontrolled ECD ($P = 0.04$) and non-small cell lung carcinoma (NSCLC) or melanoma primary histologies (compared with breast) ($P = 0.04$). No significant association was found with sex, performance status, brain metastasis number or diameter at diagnosis, index lesion diameter at diagnosis, or interval between MRI. Uncontrolled ECD, primary histology, brain metastasis number at diagnosis ($P = 0.07$), age ($P = 0.1$) and interval between diagnostic and treatment MRI ($P = 0.08$) were included in a stepwise multiple logistic regression and only the first four variables selected in the final model (see Table 2). While controlling for other variables, patients with uncontrolled ECD (adjusted odds ratio 3.21, 95% confidence interval 1.25–8.70, $P = 0.02$), patients with NSCLC (adjusted odds ratio compared with breast cancer 3.11, 95% confidence interval 1.06–10.22, $P = 0.05$) and melanoma (adjusted odds ratio compared with breast cancer 4.75, 95% confidence interval 1.55–16.28, $P = 0.01$) were more likely to experience brain metastasis growth $\geq$ 3 mm between diagnostic and treatment MRI.

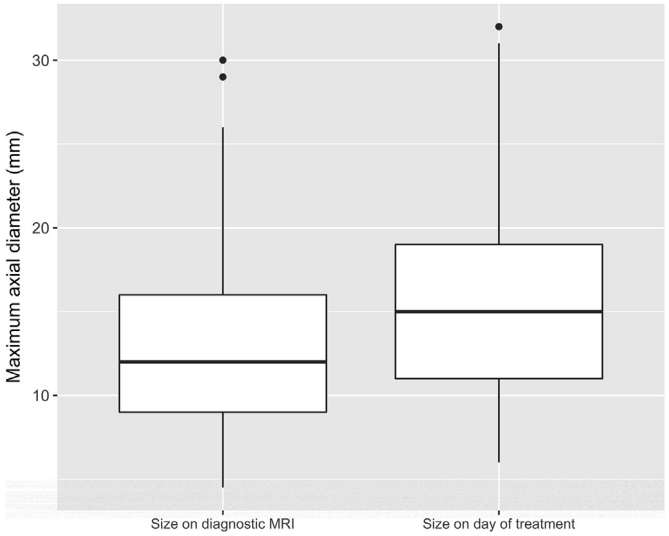

Fig 1. Box plot showing the increasing size of the index lesion (maximum axial diameter) from time of diagnostic magnetic resonance imaging (MRI) to stereotactic radiosurgery MRI. Outliers (dots) are specified as 1.5 times the upper quartile.

Change in Number of Brain Metastases

Compared with the diagnostic MRI, at least one additional brain metastasis was identified in 55 patients (35%) on SRS MRI. The mean brain metastasis number increased from 2.75 ± 3.40 to 3.74 ± 4.72. Univariate analysis found increasing brain metastasis number was associated with primary histology ($P = 0.04$) and a trend was identified for performance status ($P = 0.06$). These variables were included in a multiple logistic regression. This showed that patients with a poorer performance status (ECOG 2) were more likely to be associated with an increasing brain metastasis number on SRS MRI (adjusted odds ratio 4.04, 95% confidence interval 1.01–17.99, $P = 0.05$) compared with ECOG 0/1 but not primary histology (Table 3).

Any Clinically Significant Progression

Interval growth in the index lesion of at least 3 mm or the development of a new brain metastasis was noted in 60.2% of patients. Univariate analysis found a significant association with patient age less than 60 ($P = 0.004$). Uncontrolled ECD ($P = 0.17$) and performance status ($P = 0.12$) were also included in the multiple logistic regression. While controlling for the other variables in the model, age less than 60 years (adjusted odds ratio 4.17, 95% confidence interval 1.96–9.09, $P = 0.001$), patients with uncontrolled ECD (adjusted odds ratio 3.0, 95% confidence interval 1.08–9.43,

Table 2
Final model for growth of index lesion diameter ≥ 3 mm

Progression	Variable		Adjusted odds ratio	95% confidence interval	*P*-value
Growth in index lesion diameter ≥ 3 mm	Age		0.97	0.95–0.99	0.05
	ECD	Controlled	Reference		
		Uncontrolled	3.21	1.25–8.70	0.02
	Primary histology	Breast	Reference		
		NSCLC	3.11	1.06–10.22	0.05
		Melanoma	4.75	1.55–16.28	0.01
		Other	1.68	0.51–5.91	0.40
	Number of brain metastases at diagnosis	1	Reference		
		>1	1.76	0.88–3.60	0.12

ECD, extracranial disease; NSCLC, non-small cell lung carcinoma.

$P = 0.04$), NSCLC (adjusted odds ratio compared with breast cancer 3.43, 95% confidence interval 1.16–10.57, $P = 0.03$) and melanoma (adjusted odds ratio compared with breast cancer 3.12, 95% confidence interval 1.04–9.79, $P = 0.05$) were more likely to experience a change from time of diagnosis to time of SRS (Table 4).

Outcomes

There were 93 patients (59.6%) included in the analysis of distant intracranial control as patients with less than 3 months of follow-up were excluded. A further two patients were excluded because they progressed locally rather than distantly. A significant difference in distant intracranial control was found between patients with and without change on SRS MRI ($P = 0.046$) (Figure 2). The probability of distant intracranial control at 3 months in patients with and without changes on SRS MRI was 98.1% (95% confidence interval 94.52–100) and 100%, respectively. At 12 months, distant intracranial control was observed in 57.2% (95% confidence interval 38.9–84.2) of patients with significant change on the initial SRS MRI and 86.2% (95% confidence interval 71.96–100) without significant change). The median distant intracranial control time was not reached. There were 95 patients included in the survival analysis, with a median follow-up of 6.6 months (IQR 4.82–10.5). The median overall survival was not reached and the Kaplan–Meier estimate of probability of survival at 12 months was 59.3% (95% confidence interval 46.7–75.2%) for all patients (Figure 3). There was no significant difference in overall survival between patients experiencing clinically significant progression on the day of SRS or not.

Discussion

Patients with intracranial metastatic disease form a heterogeneous group and outcomes vary according to age, performance status, number and volume of brain metastases, ECD burden and histology [3]. The number and size of brain metastases identified on diagnostic MRI are important factors in assessing suitability for SRS, but clinically relevant intracranial progression may occur between diagnosis, SRS planning and treatment.

In our cohort, all patients underwent a repeat MRI on the day of SRS and 60% were found to have interval growth of the index lesion by at least 3 mm and/or at least one more brain metastasis. This was associated most strongly with younger age, uncontrolled ECD, NSCLC and melanoma histologies. There was ≥ 3 mm growth of the index lesion in 43% of patients. Given the steep dose gradients and small expansion margins on gross disease inherent to SRS [12], treatment to enlarging lesions could be suboptimal if based on an MRI acquired earlier [14]. At least one more metastasis was identified in 35% of patients, consistent with previous reports ranging from 29 to 38% [15–17]. This was more common in patients with poorer performance status, suggesting a link to disease burden. In other reports, associations were also made with more than four metastases on diagnostic MRI [15,17], brain metastasis size [17] and NSCLC histology [15]. In our cohort, only 22% of patients had more than four metastases and the largest brain metastasis size was 30 mm. This relatively smaller proportion and consequently low event number may account for these differences. It is noteworthy that no significant association was apparent between interval growth or more brain

Table 3
Final model for increase in number of brain metastases

Progression	Variable		Adjusted odds ratio	Confidence interval	*P*-value
Increase in number of brain metastases	Performance status	ECOG 0/1	Reference		
		ECOG 2	4.04	1.01–17.99	0.05
	Primary histology	Breast	Reference		
		NSCLC	1.7	0.62–4.93	0.31
		Melanoma	0.92	0.31–2.8	0.88
		Other	0.43	0.12–1.43	0.17

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung carcinoma.

Table 4
Final model for clinically significant progression (increase in size or number of brain metastases)

Progression	Variable		Adjusted odds ratio	Confidence interval	*P*-value
Clinically significant progression	Age	<60	Reference		
		≥60	0.24	0.11–0.51	0.001
	ECD	Controlled	Reference		
		Uncontrolled	3.0	1.08–9.43	0.04
	Primary histology	Breast	Reference		
		NSCLC	3.43	1.16–10.57	0.03
		Melanoma	3.12	1.04–9.79	0.05
		Other	1	0.33–3.06	1

ECD, extracranial disease; NSCLC, non-small cell lung carcinoma.

metastases on the day of SRS MRI and interval from the diagnostic MRI. The median scan interval in our series is consistent with others [14,18]. Selection in our cohort may have been impacted by mandating updated imaging prior to referral to the MDT, which could select out some unfavourable patients who no longer meet criteria on repeat imaging.

The association identified between clinically significant progression and inferior distant intracranial control is intuitive and probably reflects the biology of the disease. The magnitude of this difference was clinically negligible at 3 months but increased with time (see Figure 2). Further follow-up is required to investigate the association between distant intracranial control and patient or tumour factors in this cohort but predictive factors similar to those mentioned above have been reported in other studies, including younger age, no prior WBRT, uncontrolled ECD and melanoma histology [19–22]. This suggests a link between risk of future intracranial progression and more aggressive brain metastases growth kinetics. Brain metastasis velocity, defined as the cumulative number of new brain metastases since SRS, has been shown to predict for clinical outcomes such as overall survival, neurological death and need for salvage WBRT [7]. Only two patients developed a local recurrence at the time of data collection, which is less than other large institutional reviews [22] and may reflect the relatively short follow-up of the data.

In our cohort, 12 month survival was 59%. Patients treated with SRS are usually selected based on favourable prognostic factors such as controlled ECD, good performance status, young age and low volume of cerebral metastatic burden. Survival in our cohort is comparable with other studies [10,23]. There was no association between intracranial progression and overall survival as the mode of death in these select patients is often not neurological [10].

This study has the expected limitations of a retrospective, single institution review. Variation in MRI technical quality is a potential bias, because differences in magnet

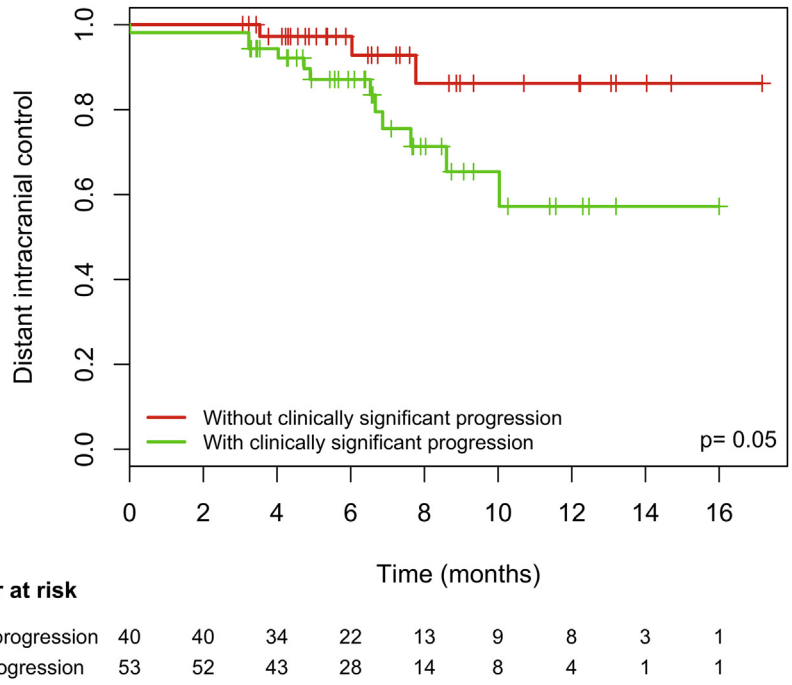

Fig 2. Log-rank comparison of distant intracranial control for patients with and without clinically significant progression on stereotactic radiosurgery magnetic resonance imaging.

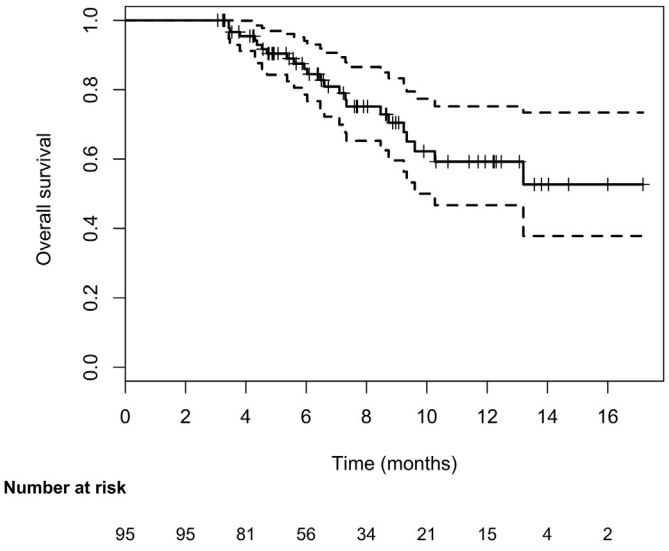

Fig 3. Kaplan–Meier curve of overall survival.

strength, slice thickness and the timing and dose of contrast between diagnostic and SRS planning scans could affect brain metastases detection [16,24]. A large portion of diagnostic MRIs were carried out external to our institution but we propose that this effect should be moderated by universal neuroradiologist review prior to SRS and good quality diagnostic scans with a median slice thickness of 1 mm. Reporting changes in brain metastases volume rather than maximum axial diameter of index lesions might be preferred, but axial diameter remains a clinically relevant consideration because target delineation is typically not carried out until a decision to treat with SRS has been made. Data relating to systemic therapy use in this cohort are lacking. Given increasing availability of small molecule targeted and immunotherapeutic agents with demonstrable intracranial activity [25,26], it is conceivable that systemic therapy could affect brain metastases growth kinetics around the time of SRS or distant intracranial control after SRS. However, such agents were most likely used in those at greatest risk of interval growth and/or new brain metastases (i.e. younger age, uncontrolled ECD, NSCLC or melanoma histology) and therefore the magnitude of this effect on the primary outcome may not be large. Exploring the impact of systemic agents with intracranial activity on brain metastasis growth kinetics before and after SRS would be a worthwhile avenue of future investigation. The follow-up in this series remains short (6.6 months), but this does not affect the primary aim of the study.

Conclusion

Intracranial progression between diagnosis and the day of SRS is common. Risk factors are uncontrolled ECD, poorer performance status, NSCLC or melanoma histologies and age less than 60 years. These patients would benefit from an MRI closer to treatment to inform patient selection and target delineation for SRS planning.

Conflict of interest

The authors declare no conflict of interest.

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