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CLINICAL STUDY

Local control after fractionated stereotactic radiation therapy for brain metastases

Selvan Rajakesari · Nils D. Arvold · Rachel B. Jimenez · Laura W. Christianson · Margaret C. Horvath · Elizabeth B. Claus · Alexandra J. Golby · Mark D. Johnson · Ian F. Dunn · Eudocia Q. Lee · Nancy U. Lin · Scott Friesen · Edward G. Mannarino · Matthew Wagar · Fred L. Hacker · Stephanie E. Weiss · Brian M. Alexander

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Abstract Stereotactic radiosurgery (SRS) is frequently used in the management of brain metastases, but concerns over potential toxicity limit applications for larger lesions or those in eloquent areas. Fractionated stereotactic radiation therapy (SRT) is often substituted for SRS in these cases. We retrospectively analyzed the efficacy and toxicity outcomes of patients who received SRT at our institution. Seventy patients with brain metastases treated with SRT from 2006–2012 were analyzed. The rates of local and distant intracranial progression, overall survival, acute toxicity, and radionecrosis were determined. The SRT regimen was 25 Gy in 5 fractions among 87 % of patients. The most common tumor histologies were non-small cell lung cancer (37 %), breast cancer (20 %) and melanoma (20 %), and the median tumor diameter was 1.7 cm (range 0.4–6.4 cm). Median survival after SRT was 10.7 months. Median time to local progression was 17 months, with a local control rate of 68 % at 6 months and 56 % at 1 year. Acute toxicity was seen in 11 patients (16 %), mostly grade 1 or 2 with the most common symptom being mild headache. Symptomatic radiation-induced treatment change was seen on follow-up MRIs in three patients (4.3 %). SRT appears to be a safe and reasonably effective technique to treat brain metastases deemed less suitable for SRS, though dose intensification strategies may further improve local control.

Keywords Brain metastases · Stereotactic radiosurgery · Stereotactic radiotherapy · Hypofractionated

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Selvan Rajakesari and Nils D. Arvold contributed equally to this work.

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S. Rajakesari · N. D. Arvold · L. W. Christianson · M. C. Horvath · S. Friesen · E. G. Mannarino · M. Wagar · F. L. Hacker · B. M. Alexander (✉)
Department of Radiation Oncology, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA, USA
e-mail: bmalexander@lroc.harvard.edu

R. B. Jimenez
Harvard Radiation Oncology Program, Boston, MA, USA

E. B. Claus · A. J. Golby · M. D. Johnson · I. F. Dunn
Department of Neurosurgery, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA, USA

E. B. Claus
Yale School of Public Health, New Haven, CT, USA

E. Q. Lee
The Center for Neuro-Oncology, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA, USA

N. U. Lin
Department of Medicine, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA, USA

S. E. Weiss
Fox Chase Cancer Center, Philadelphia, PA, USA

Introduction

Stereotactic radiosurgery (SRS) is commonly used to treat patients with brain metastases, either alone or in combination with whole brain radiation therapy (WBRT). SRS alone is associated with local control at 1 year of approximately 70–75 % [1, 2], and SRS in combination with WBRT yields a local control of approximately 80–90 % [3, 4]. This treatment is associated with relatively low toxicity, with the rates of grade 3–4 SRS-induced acute or late toxicity below 10 % in multiple series [1–3].

Not all brain metastases are suitable for SRS, however, due to the risk of increased toxicity with increasing size of the lesion [5], and the association of toxicity with the volume of brain tissue receiving greater than 12 Gy (V12) [6]. Furthermore, the threshold for toxicity of critical structures such as the optic apparatus also limits the dose that can be safely administered near these areas [7–9]. Likewise, while brainstem SRS is commonly used including at our institution [10], the doses tend to be somewhat lower than the doses used in other regions of the brain due to toxicity concerns [10–13], and there appear to be higher risks of complications with lesion volumes greater than 1 cc [12, 13]. While WBRT can be used when lesions are felt less suitable for SRS, local therapy may still be preferable in many cases, since the addition of WBRT has not been associated with a survival advantage in addition to local therapy, and is associated with greater short and long-term side effects [14].

Hypofractionated stereotactic radiation therapy (SRT) offers a potential solution, as it combines a highly localized treatment with the radiobiological therapeutic index of fractionated radiation therapy. Though this technique has been used by several centers, data regarding the outcomes and optimal dose/fractionation regimens are not as well-defined as for SRS. The objective of this study is to analyze the outcomes of patients treated with SRT at our institution, in order to determine the local control and toxicity profile of SRT for brain metastases.

Materials and methods

Patients

This retrospective study was approved by the Dana-Farber/Harvard Cancer Center institutional review board. The records of all patients (112) treated with SRT as primary treatment for a progressive brain metastasis at the Dana-Farber/Brigham and Women's Cancer Center from June 2006 to May 2012 were reviewed. The criteria generally used to select lesions for SRT as opposed to SRS at our institution included tumor size greater than 3 cm, irregular shape with V12 significantly higher than 10 cc [6], or eloquent location including immediate proximity to the optic chiasm/nerves. Patients with no radiographic follow-up after SRT or those who had received SRT after a previous surgical intervention of the lesion of interest were excluded. Seventy patients remained eligible for analysis. The diagnosis of brain metastases was made using magnetic resonance imaging (MRI); in cases where an MRI was contraindicated, diagnosis and follow-up were done using contrast CT imaging. For patients who had received multiple courses of SRT for different brain metastases, the earliest treatment was used as the basis for analysis in the study. Patients who had received or were scheduled to receive localized treatments to other brain metastases, including surgery or SRS, were included, as were patients who had previously received WBRT. SRT delivered within 3 months of receiving WBRT (the standard first imaging time point following WBRT) in the absence of clear progression was considered "concurrent" for analysis, as retrospective intent was difficult to determine. All patients had signed written consent prior to treatment in accordance with institutional policy.

Radiation therapy

Patients were immobilized using an Aquaplast^{TM} thermoplastic mask with a bite block. A frameless technique was used for treatment planning and delivery as described previously [15]. The planning CT was obtained and fused with a thin-slice contrast brain MRI performed within 2 weeks of the planned treatment time. Target volumes and organs at risk were contoured using a thin-cut T1 post-contrast sequence MRI, or a contrast-enhanced CT when MRI was contraindicated. Treatment planning was performed using BrainLAB BrainSCAN^{TM} software, and treatment was delivered using either multiple conformal arcs or static field IMRT with a Novalis^{TM} linear-accelerator based radiosurgery platform. The dose and fractionation of the treatment were chosen at the discretion of the treating physician. The dose was generally prescribed to the 90–95 % isodose line, and the planning target volume was generally covered by 99 % of the prescription dose. A stereoscopic KV X-ray system combined with infrared position tracking (ExacTrac^{TM}) was used for daily patient localization (initially version 3.5 and later version 5.0). Treatments were administered in consecutive weekday daily fractions. WBRT, when used, was administered in the standard fashion using parallel opposed beams.

Follow-up and analysis

Patients underwent an initial follow-up MRI (or CT) at 6–8 weeks, with routine follow-up every 3 months

Table 1 Baseline clinical and treatment characteristics of SRT patients

Characteristic	No. (%)
Age (years)	
Median	62
Range	30–93
KPS (%)	
60	1 (1 %)
70	10 (14 %)
80	21 (30 %)
90	22 (31 %)
100	11 (16 %)
Unknown	5 (7 %)
Histology	
NSCLC	26 (37 %)
Breast	14 (20 %)
Melanoma	14 (20 %)
SCLC	5 (7 %)
GI	4 (6 %)
RCC	4 (6 %)
Other	3 (4 %)
No. of brain metastases	
1	25 (36 %)
2	18 (26 %)
3	10 (14 %)
4	4 (6 %)
>4	13 (19 %)
Any prior WBRT	
Yes	40 (58 %)
No	30 (43 %)
WBRT within 3 months prior to SRT	
Yes	10 (14 %)
No	60 (86 %)
Location of brain metastasis receiving SRT	
Frontal	20 (29 %)
Cerebellum	19 (27 %)
Parietal lobe	9 (13 %)
Temporal lobe	7 (1 %)
Occipital lobe	4 (6 %)
Brainstem	4 (6 %)
Dural	4 (6 %)
Thalamus/basal ganglia	3 (4 %)
Maximum diameter (cm) of brain metastasis receiving SRT	
Median	1.7
Range	0.4–6.4
SRT dose/fractionation	
25 Gy/5 fx	61 (87 %)
30 Gy/10 fx	5 (7 %)
32 Gy/8 fx	2 (3 %)
33 Gy/11 fx	1 (1 %)
24 Gy/8 fx	1 (1 %)

NSCLC non-small cell lung cancer, *SCLC* small cell lung cancer, *GI* gastrointestinal, *RCC* renal cell carcinoma, *KPS* Karnofsky performance status, *WBRT* whole brain radiotherapy, *Gy* gray, *fx* fractions

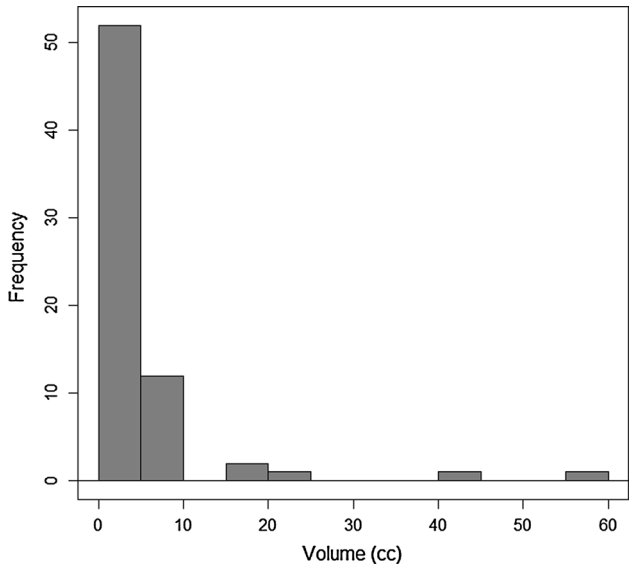

Fig. 1 Frequency distribution of tumor volumes among patients treated with SRT

thereafter. Acute toxicity was graded according to Common Terminology Criteria for Adverse Events, version 3.0. Local progression was defined as growth greater or equal to 25 % of the largest diameter of the tumor compared to pretreatment imaging. Patients were defined as having radiation necrosis if the lesion spontaneously regressed after initial growth, or if the lesion required the persistent use of steroids. In cases where the patient was taken to surgery, pathologic evidence of viable tumor was considered progression, whereas pathologic evidence of necrotic tissue in the absence of viable tumor was considered radiation necrosis. Growth of any lesions outside the index lesion treated with SRT, or interval appearance of new lesions, was considered distant progression.

The distribution of baseline patient characteristics between the treatment groups was compared using Wilcoxon rank-sum test or Fisher's exact test. Overall survival and time to local or distant progression were calculated from the date of last SRT fraction. Overall survival was estimated by the Kaplan–Meier method and compared using the log-rank test in univariate analysis. For local and distant progression, patients were censored at the time of

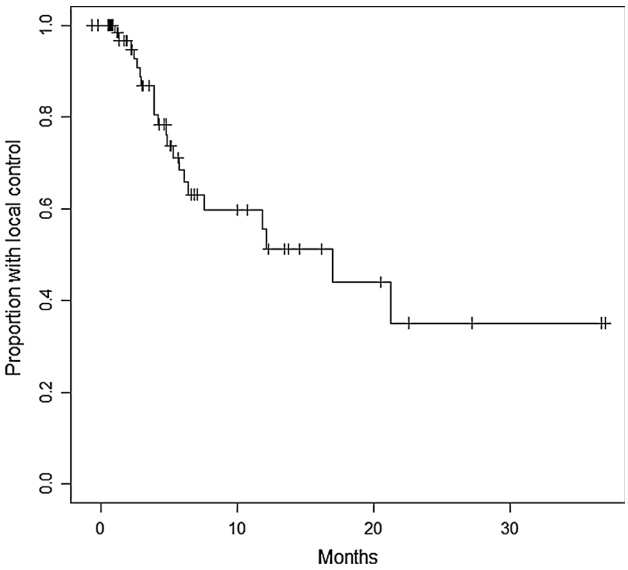

Fig. 2 Local control of brain metastases treated with SRT

their last brain MRI, at death, or if they received WBRT, for estimation by the Kaplan–Meier method. For comparative purposes, the cumulative incidence of local progression was estimated both by 1 Km, censored for death, and in a competing risk model with death as the competing risk. All reported *p*-values are based on two-sided hypothesis tests with a type I error of 0.05. Statistical analysis was computed using R version 2.11.1 including the *cmprsk* package (R package version 2.2-1).

Results

The median follow-up up was 13.5 months among surviving patients. Clinical characteristics of the 70 patients in the analysis cohort are described in Table 1. The median age was 62 years (range 30–93 years), and the most common primary tumor histologies were non-small cell lung cancer (37 %), breast cancer (20 %) and melanoma (20 %). Most patients (91 %) had a Karnofsky performance status of 70 or greater. The median tumor diameter (maximum dimension) was 1.7 cm (range 0.4–6.4 cm) and the median target volume was 2.4 cc (Fig. 1). Fifty-seven percent of patients had prior whole brain radiation, though only 14 % had WBRT within 3 months of SRT. The majority of patients (61) received a dose of 25 Gy in 5 fractions, which is the current institutional standard. However, five patients received 30 Gy in 10 fractions, two received 32 Gy in 8 fractions, one patient received 33 Gy in 11 fractions, and one patient received 24 Gy in 8 fractions.

Intracranial control

Local control was 68 % at 6 months and 56 % at 1 year, censoring for death (Fig. 2). Factors hypothesized to be associated with local control including tumor volume, dose regimen, histology, and sequential use with WBRT were not associated with control (Table 2), although there was a trend for better control with the combination of WBRT and SRT (HR 0.28; $p = 0.19$). As no variables were independently associated with local control, multivariate analysis was not performed. There was a significant competing risk of death, however, and cumulative incidence analysis of local progression with death as a competing risk yielded higher rates of local control, specifically 78 % at 6 months and 71 % at 1 year. Forty-three patients (61 %) had distant progression during their follow-up.

Overall survival

Median survival was 10.7 months; median survival according to primary tumor site was as follows: renal, 4.34 months; melanoma, 8.71 months; lung, 9.92 months; breast, 12.45 months; gastrointestinal, 12.58 months. The differences were not statistically significant. Factors found to be prognostic for survival in the graded prognostic assessment (GPA) [16] and the GPA itself were analyzed for association with survival time. KPS was significantly associated with survival ($p = 0.01$) while age ($p = 0.49$) and number of brain lesions were not ($p = 0.41$). The GPA score itself was also not prognostic, however, this assessment was limited by the number of patients within each tumor type and the lack of transferability of score between types.

Toxicity

A total of 11 patients (16 %) had acute toxicity; six patients (9 %) had grade 1 toxicity, three patients (4 %) had grade 2 toxicity, and two patients (3 %) had seizures (grade 3) in the month following treatment. The most common grade 1–2 toxicity was mild headache. The rate of symptomatic radionecrosis in the cohort was 4.3 % (n = 3), all of whom received corticosteroids but none of whom required surgical intervention.

Discussion

Here we report our experience with fractionated stereotactic radiation therapy for brain metastases. While almost all of the regimens included could be considered "hypofractionated" relative to standard radiation therapy fraction sizes (1.8 Gy, 2 Gy), the inclusions of regimens with doses

Table 2 Actuarial local control according to tumor and treatment characteristics

Characteristic	Median OS (months)	6 month actuarial LC (%)	1 year actuarial LC (%)	LR HR	95 % CI		*p*
Histology							
Breast/Lung/Gyn	10.9	67	54	1			
Melanoma/Renal/GI	10	75	62	0.77	0.28	2.1	0.62
Tumor volume							
>2.4 cc	10	70	55	1			
<2.4 cc	10.7	67	55	1.2	0.51	2.8	0.67
Concurrent WBRT							
No	10.7	64	50	1			
Yes	10.7	100	100	0.28	0.04	2.1	0.19
SRT Fractionation							
25 Gy/5 fx	10.7	68	53	1			
Other	10.5	75	75	0.44	0.06	3.3	0.43

OS overall survival, *LC* local control, *LR* local recurrence, *HR* hazard ratio, *WBRT* whole brain radiotherapy, *SRT* stereotactic radiotherapy, *Gyn* gynecologic, *GI* gastrointestinal, *Gy* gray, *fx* fractions

per fraction of 3 Gy, similar to those used in WBRT, resulted in our use simply of term 'fractionated' to distinguish from radiosurgery. While many guidelines consider regimens ≤5 fractions "radiosurgery," this distinction has ambiguous clinical and biological relevance so we use radiosurgery or SRS to refer to those regimens delivered in one fraction for clarity in our discussion. We found that SRT for brain metastases, most commonly delivered as 25 Gy in 5 fractions, was associated with an actuarial 1 year local control rate of 56 %, with minimal acute or late toxicity. In contrast, the average reported local control at 1 year for SRS alone is approximately 76 % with a published range from 48–95 %, and 82 % (range 47–100 %) for SRS in combination with WBRT. While the control rate of 56 % is generally within the range published for SRS local control, it is somewhat lower, and this could be due to several factors.

Tumor size and tumor histology are both associated with local control, and in this series, the median tumor volume was 2.36 cc, and 20 % of patients had melanoma. By virtue of increased toxicity, SRS is generally only used up to a specific maximum tumor diameter, usually conforming to the data presented in RTOG 90-05 [5], and multiple series have shown worse local control as a function of size [17–21]. For example, Elliott et al. [22] found that local control was substantially worse with tumors ≥1 cm in maximal diameter (OR 5.79, $p < 0.0001$). A plot of tumor sizes in our series is shown in Fig. 2. Overall, the distribution of tumor volumes in our cohort were relatively small, with the rationale for using SRT related to eloquent tumor location in most cases, and therefore large size was not likely a factor reducing local control. With regard to histology, approximately 5 % of patients enrolled on the RTOG 95-08 and EORTC prospective trials had melanoma [2, 3], which is significantly lower than in the present study, and this histology has been linked to greater radioresistance [23], though not in all studies [1, 4], and was not associated with more aggressive local progression in our study. A recent study found that while local control after single-fraction SRS was similar between classically radiosensitive versus radioresistant brain metastasis histologies, SRT for radioresistant histologies demonstrated worse local control than for radiosensitive histologies, with an odds ratio of 5.37 (95 % CI 3.83–6.91; $p = 0.032$) [24].

Perhaps the most important reason for lower local control seen with SRT compared to SRS is related to radiation dose. Several SRS studies have found an association between local control and dose to the tumor [17, 20, 25–27]. Unlike SRS, where the prescription dose is limited to one fraction and generally based on tumor size [5], there are a variety of different doses and fractionations reported for SRT; selected studies are summarized in Table 3. At our institution, we use 25 Gy in 5 fractions most commonly, which is the most commonly used SRT fractionation regimen used in the United States according to a national survey of radiation oncologists who treat brain metastases with SRS/SRT [28]. The average reported local control rate after SRT is approximately 78 % (range 52–100 %) [15, 29–40], though many of the studies did not specifically isolate patients who did and did not receive WBRT. Two studies directly compared SRS with SRT, and there was no significant difference in local control or survival [31, 32]. Of the studies that looked at different dosing regimens, Aoyama et.al reported an association between the isocenter dose <35 Gy or peripheral dose <32 Gy with lower local control in univariate analysis, though this factor was no longer significant in their multivariate analysis [41]. Martens et al. found that patients who received

Table 3 Summary of prior studies on SRT for brain metastases

Author	Year	# SRT Patients	Most common SRT dose/ fractionation	Prior WBRT	Median target or tumor volume	Local control at 1 year	Radionecrosis	Median survival (mo.)
Tokuuye	1998	64	42 Gy/7 fx 48 Gy/8 fx (melanoma), 52 Gy/13 fx if >3 cm or near OAR	Yes	NR	91 %	NR	8.3
Manning	2000	32	27 Gy/3 fx	Yes	Tumor volume 2.2 cc	91 % (at 6 month)	6.0 %	11.8
Aoyama	2003	87	35 Gy/4 fx	No	Tumor volume 3.3 cc	81 %	2.7 %	8.7
Lindvall	2005	47	40 Gy/5 fx	Yes	Tumor volume 5.0 cc	84 %	6.3 %	5
Ernst-Stechken	2006	51	35 Gy/5 fx 30 Gy/5 fx if WBRT	Yes	Tumor volume 6.0 cc Target volume 13.0 cc	76 %	NR	11
Fahrig	2007	150	30–35 Gy/5 fx 40 Gy/10 fx 35 Gy/7 fx	Yes	Target volume 6.1 cc	93 % (at median 28 month follow-up)	1.3 %	16
Narayana	2007	20	30 Gy/5 fx	No	Tumor volume 3.5 cc	70 %	5.0 %	8.5
Lindvall	2009	47	38 Gy/5 fx	No	Tumor volume 6.0 cc	84 % (at mean 3.7 month follow-up)	0.0 %	5
Kwon	2009	27	25 Gy/5 fx	Yes	Target volume 0.5 cc	68 %	5.8 %	10.8
Schlienger	2010	448	24–40 Gy/5 fx	Yes	Tumor volume 2.8 cc	83 %	3.1 %	8.7
Kim	2011	40	36 Gy/6 fx	Yes	Target volume 5.0 cc	69 %	0.0 %	8
Fokas	2012	122	35 Gy/7 fx 40 Gy/10 fx	No	Target volume 2.0 cc (35 Gy), 5.9 cc (40 Gy)	75 % (35 Gy) 71 % (40 Gy)	0.8 %	7 (35 Gy) 10 (40 Gy)
Martens	2012	75	30 Gy/6 fx 30 Gy/5 fx 35 Gy/7 fx	Yes	Tumor volume 1 cc Target volume 4.7 cc (upfront SRT) Tumor volume 2 cc Target volume 9.2 cc (salvage SRT)	52 %	1.3 %	9.1
Present study	2013	70	25 Gy/5 fx	Yes	Target volume 2.4 cc	56 %	4.3 %	10.7

SRT stereotactic radiotherapy, *WBRT* whole brain radiotherapy, *Gy* gray, *fx* fractions, *OAR* organs at risk, *NR* not recorded

EQD_2 >35 Gy had superior local control to those who did not (57 vs. 22 % at 1 year), though there was no significant difference in local control between the different dose concepts they examined [37]. However, in two additional studies in which several SRT doses were used, radiation dose was not associated with local control or survival [31, 33]. Dose regimen was not associated with local control or survival in our study, but the variability in dosing regimens was minimal and certainly too small for meaningful comparisons. Furthermore, the competing risk of death makes comparison of local control among any variable group problematic due to small numbers. The most common dose used in our study and nationally, 25 Gy in 5 fractions, yields an EQD_2 of 31.25 Gy, which could be associated with the somewhat lower local control seen compared to some of the published data (Table 4; Electronic Supplementary File). A randomized trial would be necessary to properly evaluate different dose regimens to determine the best SRT regimen both with regards to local control and toxicity.

Additional reasons for variation in the reported local control rates across SRT and SRS studies are methodologic. Specifically, different studies use varying criteria or methods to estimate local control. First, local progression is often defined differently in each study, including variations in both size criteria and methods for determining

progression versus radiation treatment effect, and modifying these definitions could lead to very different results. We have used an increase of greater than 25 % in the largest tumor diameter, as this has been the measure used in prior studies from our institution [42, 43]; however, other groups have used alternative definitions with either one-dimensional or volumetric parameters. Such variation creates difficulty in comparing outcomes. A second challenge lies in the analysis methods used across studies of SRT, specifically, how local control is estimated, in the setting of patients with brain metastases having a high competing risk of death. In our results, we found local control estimates to be significantly lower (56 % at 1 year) if we censored at the time of death using the Kaplan–Meier method, as compared to local control rates when treating death as a competing risk (71 % at year). It is not always clear which type of analyses were performed in previous SRT studies; some have relatively clear descriptions of the use of Kaplan–Meier methods for the assessment of local control where death is presumably censored in a non-informative manner [37, 41]. Others may report response rates [30], which have results more like competing risk models, as stable disease at 3 months followed by death at 4 months would count as stable disease with no time component and overestimate local control relative to Kaplan–Meier. Most studies, however, do not describe in detail the analysis procedures for assessing local control, so it is impossible to make confident comparisons of local control between various SRT studies. Our analysis showing local control of 71 % when analyzed as death as a competing risk compares favorably to SRS and may be the most clinically relevant endpoint, especially when considering the low toxicity seen with SRT.

Given that SRT is typically employed when tumor sizes are too large for SRS or the location is eloquent, we found that the rates of toxicity were reassuringly low in our cohort. The acute toxicity rate in this study was 16 %, and the rate of symptomatic radiation treatment effect was 4 %. In comparison, the average rate of toxicity reported for SRS is approximately 16 % (range 0–64 %), and 11 % for SRT (range 0–39 %). The average rate of radiation treatment effect in the studies analyzed is 5 % for SRS (range 0.7–24 %) and 3 % (range 0–6.25 %) for SRT. In general, the rates of toxicity appear to be comparable between SRS and SRT, and SRT may in fact be less toxic [31, 32]. Similar to SRS, both tumor volume and dose appear to be correlated with toxicity after SRT. Ernst-Stecken et al. [29] found that the median target volume of treated lesions that were complicated by radiation treatment effect was 16.75 cc compared to a median of 8.20 cc for all other cases. There was also a correlation between radiation treatment effect and the volume of normal brain receiving more than 4 Gy per fraction; only 14 % of patients had radiation treatment effect if $V_{4\ Gy}$ was <23 cc versus 70 % if it was higher. While our data compares favorably with the reported literature, measurement and attribution of toxicities are notoriously difficult due to definitional and measurement variability.

A significant limitation of this study and others reporting on radiation for brain metastases is the determination of necrosis versus progression. We, like others, have attempted to mitigate this through retrospective biased analysis of the natural history of the lesions- with spontaneous regression felt to be much more likely associated with "necrosis" rather than true tumor progression. Even so, misclassification is an enormous potential source of error for studies of radiation dose and fractionation that will hopefully be reduced in the future with advanced imaging techniques.

In conclusion, SRT appears to be a safe and reasonably effective treatment option for patients with brain metastases who would otherwise not be candidates for SRS, though with slightly lower local control in this series. Given the relatively small size of the tumors in our cohort and the lack of a clear association of tumor histology with control, the lower control rate was more likely due to lower equivalent dose or varying definitions of local control. Dose fractionation schemes delivering higher equivalent dose may be appropriate or consideration of surgical resection/debulking followed by SRT may be appropriate when possible. Ultimately, randomized prospective data will be necessary to determine if local control truly differs between SRT and SRS, and to discern the optimal dose and fractionation for SRT.

Conflict of interest None.

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