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CLINICAL STUDY

Hypofractionated radiosurgery has a better safety profile than single fraction radiosurgery for large resected brain metastases

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Abstract The purpose of this study is to compare the safety and efficacy of single fraction radiosurgery (SFR) with hypofractionated radiosurgery (HR) for the adjuvant treatment of large, surgically resected brain metastases. Seventy-five patients with 76 resection cavities ≥ 3 cm received 15 Gray (Gy) × 1 SFR (n = 40) or 5–8 Gy × 3–5 HR (n = 36). Cumulative incidence of local failure (LF) and radiation necrosis (RN) was estimated accounting for death as a competing risk and compared with Gray's test. The effect of multiple covariates was evaluated with the Fine-Gray proportional hazards model. The most common HR dose-fractionation schedules were 6 Gy × 5 (44 %), 7–8 Gy × 3 (36 %), and 6 Gy × 4 (8 %). The median follow-up was 11 months (range 2–71). HR patients had larger median resection cavity volumes (24.0 vs. 13.3 cc, p < 0.001), planning target volumes (PTV) (37.7 vs. 20.5 cc, p < 0.001), and cavity to PTV expansion margins (2 vs. 1.5 mm, p = 0.002) than SFR patients. Cumulative incidence of LF (95 % CI) at 6 and 12-months for HR versus SFR was 18.9 % (0.07–0.34) versus 15.9 % (0.06–0.29), and 25.6 % (0.12–0.42) versus 27.2 % (0.14–0.42), p = 0.80. Cumulative incidence of RN (95 % CI) at 6 and 12 months for HR vs. SFR was 3.3 % (0.00–0.15) versus 10.7 % (0.03–0.23), and 10.3 % (0.02–0.25) versus 19.2 % (0.08–0.34), p = 0.28. On multivariable analysis, SFR was significantly associated with an increased risk of RN, with a HR of 3.81 (95 % CI 1.04–13.93, p = 0.043). Hypofractionated radiosurgery may be the more favorable treatment approach for radiosurgery of cavities 3–4 cm in size and greater.

Keywords Hypofractionated · Radiosurgery · Brain · Central nervous system · Metastases

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Introduction

Adjuvant radiation therapy is critical to providing local control of surgically resected brain metastases. The use of whole brain radiation therapy (WBRT) following surgical resection is considered standard of care, as two prospective randomized trials have demonstrated a significant reduction in local tumor recurrence from 46–59 % with observation to 10–28 % with WBRT [1, 2]. However, given the recognized neurocognitive sequelae of WBRT [3] and the lack of a survival benefit with its use [1, 2], tumor bed radiosurgery alone has been increasingly utilized to provide local control while sparing patients the toxicities of WBRT.

Multiple retrospective series reporting excellent local tumor control support the use of radiosurgery to the tumor bed [4, 5]. Most commonly, these series have employed single fraction radiosurgery (SFR) techniques with dosing based on tumor bed size in accordance with Radiation

Therapy Oncology Group (RTOG) 90-05 [6]. RTOG 90-05 was limited to tumors ≤4 cm in diameter, and established the maximum tolerated dose of 15 Gy for lesions 3.1–4.0 cm in size. Even with this radiosurgery dose, the risk of unacceptable central nervous system toxicity for tumors >3 cm was found to be 16 times that of lesions ≤2 cm in size in this prospective study. Due to this report and others similarly demonstrating an increased risk of post-treatment edema with SFR for large intracranial lesions [6–9], hypofractionated radiation dose schedules have been suggested as an alternative to improve the toxicity profile.

Multiple institutions have reported favorable outcomes with the use of hypofractionated radiosurgery (HR) for cavities 3–4 cm in size and greater [10–14]. However, the safety and efficacy of HR has not previously been directly compared with SFR for resected brain metastases of this size. The purpose of this analysis is to compare local tumor control (LC) and the incidence and severity of radiation necrosis (RN), among patients treated with either SFR or HR for brain metastasis resection cavities ≥ 3 cm in diameter.

Methods and materials

Patient selection

The use of tumor bed radiosurgery alone was generally reserved for patients with favorable characteristics, including Karnofsky performance status (KPS) ≥70 %, recursive partitioning analysis (RPA) Class I or II [15], and one to three brain metastases, or for patients with progressive local disease following previous WBRT. Initially, SFR was used for the majority of all cavities up to 4 cm in diameter, and HR was reserved for patients who were not considered acceptable candidates for SFR due to cavity size > 4 cm, close proximity to critical structures, or history of previous radiation treatment that was considered to put the patient at increased risk of treatment toxicity. Beginning in July 2011 and then September 2012, respectively, patients were offered enrollment in one of two prospective institutional trials of either SFR (applicable to cavities up to 4 cm in size, NCT01395407) or HR (applicable to 3 cm in size and greater, NCT01705548).

For the purpose of this analysis, outcomes among patients treated either on or off trial with SFR for cavities 3–4 cm in diameter are retrospectively compared to outcomes for patients treated with HR for cavities 3 cm in size or greater. After institutional review board approval, patient records were searched to identify patients treated at Emory University with either SFR or HR (in 2–5 fractions) for a diagnosis of brain metastases between January 2007 and June 2014. Patients who were planned to receive combined WBRT and radiosurgery boost were not included, nor were patients with radiosensitive tumors such as small-cell cancer, lymphoma, or seminoma. Only patients treated following surgical resection with cavities at least 3 cm in the largest dimension and with at least 1 month of follow-up surveillance imaging were included for analysis.

Treatment technique

SFR and HR were delivered according to the radiosurgery techniques previously described [5, 10]. A high-resolution MRI with and without contrast was acquired for treatment planning immediately before CT simulation for each patient, unless there was a contraindication to undergoing MRI (n = 1). At the time of simulation, patients were immobilized with a stereotactic head frame (Brainlab, Feldkirchen, Germany) placed by the neurosurgical team, or with an Aquaplast mask (WFR/Aquaplast Corporation, Wyckoff, NJ) if a frameless technique was used. A high-resolution, thin-slice (0.625-mm slice thickness) CT scan without contrast was obtained for treatment planning on the day of radiosurgery for framed procedures and up to 4 days prior for frameless procedures. The treatment planning MRI was registered to the simulation CT using BrainScan or iPlan (Brainlab) or Velocity AI (Varian, Palo Alto, CA) software. Delineation of gross tumor volume (GTV) was made to include the entire resection cavity plus any remaining enhancing tumor.

For SFR, the planning target volume (PTV) included the GTV plus 0–2 mm margins, per physician judgment, to account for patient setup and target motion uncertainty. Since 2008, 2 mm margins were made standard to account for uncertainty in resection cavity delineation. The prescribed dose of 15 Gy was used for SFR according to RTOG protocol 90-05 [6].

For HR, the PTV included the GTV plus a 1–10 mm margin, per physician judgment. Most often, a GTV to PTV margin of 2 mm was used, though 10 mm was used in one case to account for additional uncertainty for a patient who could not undergo MRI. Radiation dose and fractionation were prescribed per the treating physician's discretion prior to 2012, after which 6 Gy × 5 became the standard departmental hypofractionation schedule. HR patients uniformly were treated with a frameless radiosurgery technique.

For both SFR and HR, treatment was delivered with either intensity-modulated static fields (IMRS), volumetric modulated arc therapy (VMAT) or dynamic conformal arcs (DCA). IMRS or VMAT was prescribed so that at least 95 % of the PTV received at least 100 % of the prescribed dose, and DCA therapy was prescribed at the 80 % isodose line. All SFR and HR procedures were carried out with

either the Trilogy™ or Novalis Tx™ linear accelerators (Varian Medical Systems, Palo Alto, CA). For frameless single fraction or HR treatments, Cone beam CT (CBCT) scans with 6° of freedom registration allowed for precise positioning prior to treatment [16, 17].

For comparison of single and multiple dose regimens, radiation dose was converted to biological equivalent dose (BED) [18] and single fraction equivalent dose (SFED) [19] according to the formulas below, assuming an α/β ratio of 10 for tumor control, and where D is total dose, d is dose per fraction and Dq is 1.8 [19].

$$BED_{10} = D \times [1 + d/(\alpha/\beta)]$$

$$SFED = D - (n - 1) \times Dq$$

Follow-up and outcomes analysis

Patients were followed with history, physical examination, and MRI imaging (when feasible) with and without contrast, initially 4–6 weeks after radiation treatment completion, and then every 3 months thereafter. Local failure and distant intracranial failure were defined by MRI-detected intracranial tumor recurrence or progression. Local failure was defined as greater than 90 % of tumor recurrence within the prescription isodose volume, whereas recurrence outside of that volume was defined as distant intracranial failure. Local and distant intracranial failures were recorded irrespective of first site of failure. RN was diagnosed by increased enhancement on T1 post-contrast MRI with or without abnormal T2/FLAIR signal abnormality that did not rapidly progress on serial imaging, was associated with hypoperfusion on dynamic susceptibility contrast (DSC) enhanced MRI, or was confirmed by surgical resection and pathologic analysis. RN was graded according to the Common Terminology Criteria for Adverse Events version 3.0 [20]. For patients with uncertainty regarding the diagnosis of tumor progression or RN, cases were frequently reviewed at Adult Brain Tumor Conference meetings to arrive at a consensus diagnosis.

Statistical analysis

Patient's characteristics were summarized and compared between those treated with SFR or HR by Wilcoxon rank-sum test for numerical covariates and chi-square test or Fisher's exact test for categorical covariates, where appropriate. Covariates analyzed included age at treatment, gender, primary tumor histology, RPA class [15], gross-total resection (GTR) versus sub-total resection (STR), interval between surgery and RT, GTV volume, PTV volume, GTV-to-PTV margins, total radiation dose, SFED, BED$_{10}$, and history of prior or salvage WBRT.

Survival functions were estimated by the Kaplan–Meier method [21] and a log-rank test is used to assess the difference in OS for patients treated with HR and SFR. OS was censored at last follow-up for living patients. The cumulative incidence functions of LF, RN and symptomatic RN were estimated using death without the event of interest as a competing risk. The difference in cumulative incidence rates between patients treated with HR and SFR was examined with the Gray's test [22]. The Cox [23] or Fine-Gray [24] proportional hazards model was employed, as appropriate, to estimate the effect of HR vs. SFR and other covariates on the outcome variables. Multivariable survival analysis was carried out by entering all covariates of interest in a model and using a backward variable selection method with an alpha level of removal of 0.2. SFR vs. HR was forced in the model. All analyses are done using SAS 9.3 (SAS Institute, Inc., Cary, North Carolina) with a significant level of 0.05.

Results

Patient and tumor characteristics

Analysis included 75 patients with 76 resection cavities treated with 15 Gy × 1 fraction SFR (n = 40) or 5–8 Gy × 3–5 fractions HR (n = 36). Patient, tumor and treatment characteristics are listed in Table 1. HR patients were more likely to have a larger median resection cavity volume (24.0 vs. 13.3cc, p < 0.001), PTV volume (37.7 vs. 20.5cc, p < 0.001), and cavity to PTV expansion margins (2 vs. 1.5 mm, p = 0.002) than SFR patients. The median SFED and BED$_{10}$ were significantly greater with HR as compared with SFR; 21.6 vs. 15 (p < 0.001) and 45.6 versus 37.5 (p = 0.006), respectively. The most common HR dose-fractionation schedules used were 6 Gy × 5 (44 %), 7–8 Gy × 3 (36 %), and 6 Gy × 4 (8 %).

Intracranial tumor control and patters of failure

Follow-up time was similar in both HR and SFR cohorts (p = 0.651), with a median (range) total follow-up of 11 months (2–71) for all patients, and a median MRI surveillance follow up time of 8 months (1–64). There was no difference in local control according to whether HR or SFR were used. Cumulative incidence of LF (95 % CI) at 6 and 12 months for HR vs. SFR was 18.9 % (0.07–0.34) versus 15.9 % (0.06–0.29), and 25.6 % (0.12–0.42) versus 27.2 % (0.14–0.42), p = 0.80 (Fig. 1). On univariable analysis, only increasing GTV volume was significantly associated with LF (p = 0.014), though there was also a trend for an association between increasing PTV volume (p = 0.084) and RPA class 3 patients (p = 0.079). After accounting for other prognostic variables on multivariable

Table 1 Patient and treatment characteristics

Characteristic		SFR (n = 40) n (%)	HR (n = 36) n (%)	P value*
Age	Mean (±SD)	52.83 (±14.21)	57.86 (±11.93)	0.101
Gender	Female	24 (60)	20 (55.6)	0.695
	Male	16 (40)	16 (44.4)	
Primary site	Breast	6 (15)	9 (25)	0.460
	Lung	15 (37.5)	14 (38.9)	
	Others	19 (47.5)	13 (36.1)	
RPA class	1/2	39 (97.5)	23 (63.89)	<0.001
	3	1 (2.5)	13 (36.11)	
GTR versus STR	GTR	27 (67.5)	20 (55.6)	0.284
	STR	13 (32.5)	16 (44.4)	
SFED	Median (range)	15 (15–15)	21.6 (17.4–25.3)	<0.001
BED10	Median (range)	37.5 (37.5–37.5)	45.6 (35.7–53.63)	0.006
GTV to PTV margin	Median (range)	1.5 (1–2)	2 (1–10)	0.002
GTV	Median (range)	13.3 (3.1–27.6)	23.95 (9.1–57)	<0.001
PTV	Median (range)	20.5 (7.1–38.3)	37.7 (12.7–80)	<0.001
Time from surgery to RT (days)	Median (range)	32 (15–86)	35.5 (18–266)	0.295
Previous or salvage WBRT	No	33 (82.5)	25 (69.4)	0.181
	Yes	7 (17.5)	11 (30.6)	
	Previous	1	6	
	Salvage	6	5	

RPA recursive partitioning analysis, *GRT* gross-total resection, *STR* sub-total resection, *SFED* singe fraction equivalent dose, *BED* biological equivalent dose, *GTV* gross tumor volume, *PTV* planning target volume

* P value is calculated by Wilcoxon rank-sum test for numerical covariates; and chi-square or Fisher's exact test for categorical covariates, where appropriate

Fig. 1 Cumulative incidence curves of local tumor failure among the hypofractionated radiosurgery (HR) and singe fraction radiosurgery (SFR) cohorts
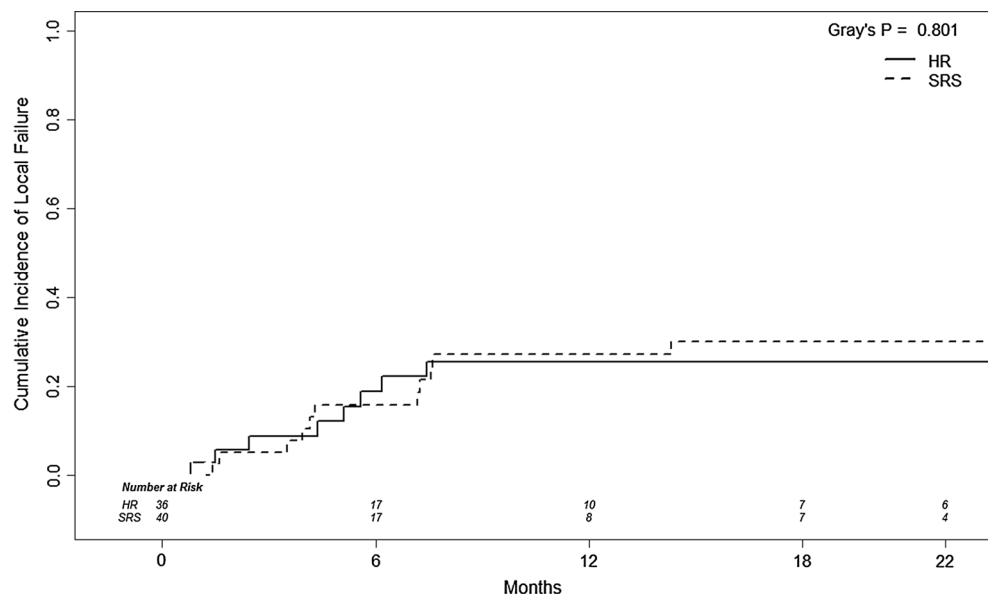
analysis, increasing GTV volume remained significantly associated with local failure (p = 0.024), as did the history of previous or salvage WBRT (p = 0.031). Additionally, there was a trend between higher RT dose and decreased LF (p = 0.078). All variables included in the multivariable analysis are listed in Table 2.

Local failure was a component of first failure in 11 (27.5 %) SFR patients and 8 (22.2 %) HR patients at a median time of 4.1 months (0.2–14.3) and 4.8 months (0.8–7.4), respectively. Salvage cranial RT was received by 16 (69.6 %) HR patients with intracranial progression, and included WBRT in 6 patients and SFR to distant sites in 10 patients. Among the SFR cohort, 15 (57.7 %) patients received salvage cranial RT, including WBRT in 9 patients and SFR to distant sites in 6 patients.

Radiation necrosis

The cumulative incidence of RN (95 % CI) at 6 and 12 months for HR vs. SFR was 3.3 % (0.00–0.15) versus 10.7 % (0.03–0.23), and 10.3 % (0.02–0.25) versus 19.2 % (0.08–0.34), p = 0.28 (Fig. 2). There were no significant predictors of RN on univariable analysis. However, on multivariable analysis, SFR was associated with a significantly increased risk of RN, with a hazard ration of 3.81 (95 % CI 1.04–13.93, p = 0.043). Female gender (p = 0.030) and older age at treatment (p = 0.046) were also independent predictors of radiation necrosis (Table 2).

In total, 12 (30 %) SFR patients experienced RN at a median (range) time of 9.0 months (1.1–44.9) after treatment, compared with only 5 (14 %) HR patients at a median time of 7.4 months (5.2–40.9). Among the 5 HR patients with RN, 3 patients received 7 Gy × 3 fractions and 2 patients received 6 Gy × 5 fractions. The incidence and severity of RN experienced by patients treated with HR versus SFR is listed in Table 3. A higher proportion of patients treated with SFR experienced symptomatic (≥grade 2) or severe (grade 3–4) RN as compared to patients treated with HR (20 vs. 6 %, and 10 vs. 0 %, respectively). Both HR patients with grade 2 RN had received prior WBRT 15 and 11 months before HR. Among the SFR cohort, one patient with grade 1 RN had received salvage WBRT 8 months after SFR and 5.4 months prior to RN diagnosis. An additional 2 patients with grade 2 RN had received salvage WBRT 6–18 months after SFR and 2–7.6 months prior to RN diagnosis. Among the 4 patients with grade 3–4 RN in the SFR cohort, two required advanced medical management such as bevacizumab or hyperbaric oxygen plus pentoxifylline and vitamin E for severe symptoms (grade 3), one required hospitalization and high-dose dexamethasone (grade 3), and one required intensive care unit admission and intubation (grade 4). None of the patients with grade 3–4 RN had received prior or salvage WBRT. In comparison, no HR patients experienced RN greater than grade 2.

The cumulative incidence of symptomatic RN at 6 and 12 months for HR vs. SFR was 3.3 % (0.00–0.14) versus 10.7 % (0.03–0.23) and 6.8 % (0.01–0.02) versus 16.4 % (0.06–0.30), p = 0.116 (Fig. 2). On univariable analysis, there were no significant predictors of symptomatic RN, though there was a trend for an increased risk with SFR (p = 0.106). On multivariable analysis, only female gender was significantly associated with an increased risk of symptomatic RN (p = 0.041), though the trend with SFR persisted (p = 0.084).

Table 2 Multivariable analysis	Outcome and variable	Hazard ratio (95 % CI)	P value
	Local failure		
	SFR versus HR	0.82 (0.09–7.18)	0.859
	GTV volume	1.06 (1.01–1.11)	0.024
	Total RT dose	0.86 (0.73–1.02)	0.078
	RPA class 1/2 vs. 3	0.36 (0.05–2.43)	0.293
	Time from surgery to RT	0.97 (0.94–1.01)	0.166
	Previous or salvage RT versus none	2.73 (1.09–6.82)	0.031
	Radiation necrosis		
	SFR versus HR	3.81 (1.04–13.93)	0.043
	Male versus female	0.36 (0.14–0.90)	0.030
	GTV volume	1.04 (0.99–1.10)	0.148
	Age	1.03 (1.00–1.05)	0.046
	Symptomatic radiation necrosis		
	SFR versus HR	3.79 (0.83–17.24)	0.084
	Male versus female	0.13 (90.02–0.92)	0.041

Fine-Gray proportional subdistribution hazards models were employed. Backward variable selection method with an alpha level of removal of 0.2 was used. When not included, the following variables were removed from the model: age, gender, primary site, GTR vs. STR, GTV volume, GTV to PTV margin, Total RT Dose, BED, and previous or salvage WBRT. *Note* SFR versus HR was forced in the mode

Fig. 2 Cumulative incidence of radiation necrosis (top) and symptomatic radiation necrosis (bottom) among the hypofractionated radiosurgery (HR) and singe fraction radiosurgery (SFR) cohorts
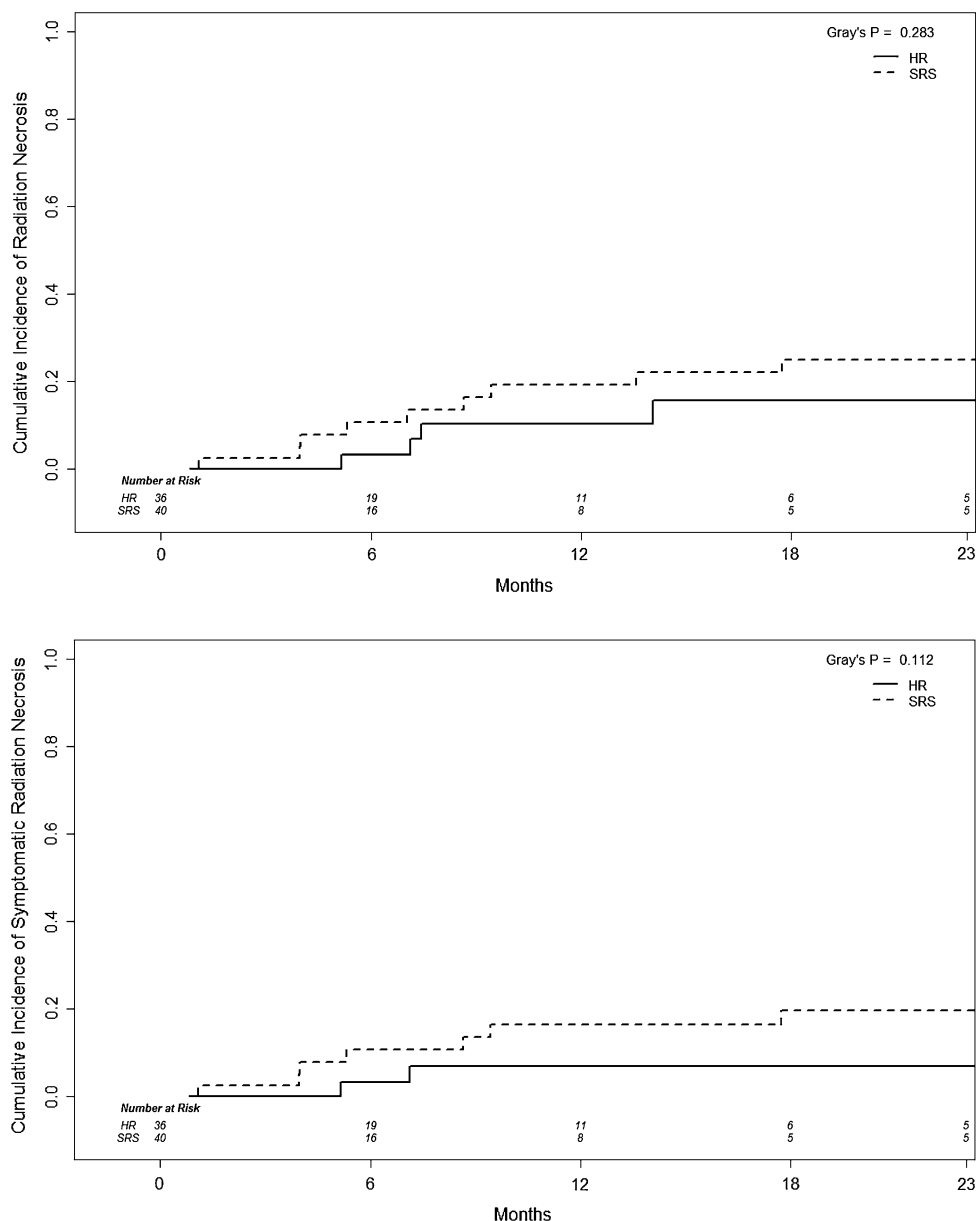
Overall survival

Median OS time in all patients was 11.2 months (95 % CI 8.9–7.4). There was no significant difference in OS among the two cohorts, with 6 and 12 month KM estimates (95 % CI) of OS for HR versus SFR of 71.6 % (0.52–0.84) versus 66.7 % (0.49–0.79), and 54.9 % (0.36–0.70) versus 41.1 % (0.26–0.56), p = 0.308.

Discussion

The results of this study demonstrate that the use of SFR for resected brain metastases 3–4 cm in size is associated with an increased risk of radiation necrosis compared with

the use of HR, delivered in 3–5 fractions, for lesions ≥3 cm. No difference in local control among patients treated with either modality was found. HR appears may be the more favorable treatment modality with a reduced toxicity profile, despite the fact that patients in the HR group tended to have larger GTV and PTV volumes, which could be expected to predispose the HR cohort to an increased risk of local failure and treatment toxicity [9, 10, 25].

The present study adds to the current literature by specifically reporting both radiographic and symptomatic radiation necrosis rates among patients treated with SFR and HR for cavities ≥3 cm in diameter, as this data is currently limited. Previously reported series of tumor bed radiosurgery have most commonly included smaller target volumes and have not reported toxicity according to tumor

Table 3 Incidence and severity of radiation necrosis

Radiation necrosis	SFR (n = 40)	HR (n = 36)
	n (%)	n (%)
Total	12 (30 %)	5 (13.8 %)
Grade		
1	4 (10 %)	3 (8.3 %)
2	4 (10 %)	2 (5.6 %)
3	3 (7.5 %)	0
4	1 (2.5 %)	0
Received previous or salvage RT	3*	2**

SFR single fraction radiosurgery ,*HR* hypofractionated radiosurgery, *WBRT* whole brain radiation therapy

* One SFR patient with grade 1 RN and 2 SFR patients with grade 2 RN had received salvage WBRT

** Two HR patients with grade 2 RN had each received prior RT

size. One recently published series from Brennan et al., which did separately analyzed outcomes with SFR for cavities >3 cm (n = 23), reported a 13 % incidence of pathologically proven radiation necrosis, though total radiation necrosis rates was not reported or graded [24]. In the only other study, to our knowledge, to have previously compared the use of SFR and HR among resection cavities, Broemme et al. evaluated 41 cavities treated with either technique and reported only one case of histologically proven RN in the SFR cohort [26]. The target volumes included in this study were of smaller median size than the present analysis (median PTVs for SFR and HR of 17cc and 21 cc versus 21 cc and 37 cc in the current study), and rates of radiographic and clinically significant symptomatic RN were again not reported [26]. The 30 % total incidence, of radiographic (10 %) and symptomatic (20 %) RN among the SFR cohort in this analysis is an important finding that has not previously been reported in the literature for resection cavities of this size.

It is important to note that patients were included in this analysis regardless of whether they received radiosurgery only or radiosurgery plus prior or salvage WBRT. The authors felt it was important to include patients who received WBRT as this is a common scenario with the use of radiosurgery in clinical practice. However, the increased risk of radiation necrosis in the SFR cohort compared to the HR cohort cannot be explained by the addition of WBRT. A greater proportion of HR patients received prior or salvage WBRT than did the SFR patients (31 vs. 18 %). Furthermore, the addition of prior or salvage of WBRT was not found to be associated with an increased risk of radiation necrosis on either univariable or multivariable analysis.

The local control among the SFR and HR cohorts in this series is comparable with the published literature. The cumulative incidence of local failure at 1 year was 26 and 27 % for HR and SFR patients, respectively, in this series. Brennan et al. reported a similar LF rate of 31 % at 12 months [27] with the use of SFR among cavities >3 cm, and an even higher LF rate of 54 % was found when looking specifically at superficial cavities >3 cm [27]. While local failure rates with the use of SFR for smaller size cavities treated to higher doses have ranged from 0–26 % at 1 year [4, 5], our results are not surprising given the known poor prognostic factor of increasing tumor size [28]. Similarly, past HR series have reported 1 year LF ranging from 7–29 % [11, 13, 29, 30]. These results are also comparable to the 10–28 % local failure rates observed after WBRT [1, 2], and continue to support the use of focal radiation therapy for these large lesions. In this study, increasing GTV size was also a significant independent predictor for increases local control, which highlights the need for optimization of local control with large intracranial lesions. Given the increased toxicity of SFR for large resection cavities demonstrated here, there seems more opportunity to improve local control without excessive toxicity by dose escalating the HR treatment. Indeed, a trend between increased RT dose and reduced incidence of local failure was demonstrated on multivariable analysis in this report. A phase I dose escalation study is currently underway at Emory University (NCT01705548), using the most common dose-fractionation scheme in this study, 6 Gy × 5, as the entry dose level.

This study is limited by the retrospective study design and unknown bias in treatment selection. However, considering HR was more often used in patients with larger resection cavities and among more patients who had previously received radiation therapy to the treatment site, one may expect bias to favor better outcomes in SFR group rather than the HR group. Additional limitations exist regarding the diagnosis of radiation necrosis by imaging characteristics alone, attributing symptoms to radiation necrosis in patients with existing intracranial pathology, and the limited follow-up time of 11 months, as radiation necrosis may occur even later. Further, the heterogeneity of dose-fractionation schedules used within the HR cohort may limit the ability to draw conclusions about the safety and efficacy of a particular fractionation schedule. However, an important finding was the high proportion of patients with radiation necrosis who experienced severe grade 3–4 symptoms in the SFR cohort (4 of 12, 33 %), while no patients in the HR group experienced more than mild symptoms requiring short-term medical management. These results should be interpreted with caution given the small number of events in each cohort and the limited patient sample size.

In conclusion, hypofractionated radiosurgery appears to be better tolerated that single fraction radiosurgery for

resected large brain metastases ≥3 cm in size. Hypofractionated radiosurgery is associated with a reduced risk of symptomatic radiation necrosis while providing equivalent tumor control. The investigators therefore recommend the use of HR for resection cavities of this size to minimize toxicity risk with local therapy. Dose optimization of HR is warranted in a prospective fashion, given the variable dose and fractionation schedules used in this series and in others.

Conflict of interest Ian Crocker serves as a consultant for Varian Medical Systems (Varian, Palo Alto, CA).

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