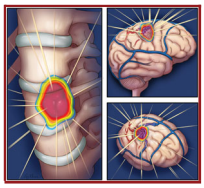

The use of Hypofractionated Radiosurgery for the Treatment of Intracranial Lesions Unsuitable for Single-Fraction Radiosurgery

Jim Zhong, MD*
Robert H. Press, MD*
Jeffrey J. Olson, MD‡
Nelson M. Oyesiku, MD, PhD‡
Hui-Kuo G. Shu, MD, PhD*
Bree R. Eaton, MD*

*Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, Georgia; ‡Department of Neurosurgery, Emory University, Atlanta, Georgia

Correspondence:
Jim Zhong, MD,
Department of Radiation Oncology,
Emory University,
1365 Clifton Rd NE, Room AT225,
Atlanta, GA 30322.
E-mail: Jim.Zhong@emory.edu

Received, September 7, 2017.
Accepted, March 22, 2018.
Published Online, April 28, 2018.

Stereotactic radiosurgery (SRS) is commonly used in the treatment of brain metastases, benign tumors, and arteriovenous malformations (AVM). Single-fraction radiosurgery, though ubiquitous, is limited by lesion size and location. In these cases, hypofractionated radiosurgery (hfSRS) offers comparable efficacy and toxicity. We review the recent literature concerning hfSRS in the treatment of brain metastases, benign tumors, and AVMs that are poorly suited for single-fraction SRS. Published retrospective analyses suggest that local control rates for brain metastases and benign tumors, as well as the rates of AVM obliteration, following hfSRS treatment are comparable to those reported for single-fraction SRS. Additionally, the toxicities from hypofractionated treatment appear comparable to those seen with single-fractioned SRS to small lesions.

KEY WORDS: Hypofractionated, SRS, Radiosurgery, Brain metastases, Acoustic neuroma, Vestibular schwannoma, Arteriovenous malformations, Benign tumors

Neurosurgery 83:850–857, 2018 DOI:10.1093/neuros/nyy145 www.neurosurgery-online.com

Stereotactic radiosurgery (SRS) has been widely adopted into modern radiation therapy. Common uses include the treatment of brain metastases, benign tumors such as meningiomas and acoustic neuromas, and arteriovenous malformations (AVM). While single-fraction radiosurgery is more commonly utilized in the treatment of these types of lesions, its therapeutic index is reduced when lesions are large (often defined as ≥3 cm diameter or approximately 14 cc volume) or are located in close proximity to critical structures. In such cases, hypofractionated radiotherapy (hfSRS) has emerged as an alternative treatment strategy used to achieve comparable efficacy while minimizing toxicity, and is made possible by the technical development of frameless radiosurgery techniques that allow for multifraction treatment with precision and accuracy similar to a framed radiosurgery approach. We review the use of hfSRS in the treatment of brain metastases, benign tumors, and AVMs.

ABBREVIATIONS: AVM, arteriovenous malformations; **BED,** biologically effective dose; **hfSRS,** hypofractionated radiosurgery; **RTOG,** Radiation Therapy Oncology Group; **SRS,** Stereotactic radiosurgery

BRAIN METASTASES

Given the neurotoxicity associated with whole-brain irradiation, the use of SRS is often preferred to minimize treatment-related neurocognitive decline while preserving tumor control.[1,2] The maximal tolerated doses of single-fraction SRS to brain lesions up to 4 cm in size were defined by the Radiation Therapy Oncology Group (RTOG).[3] Subsequent randomized studies have demonstrated the local control benefit of SRS for intact brain metastases and resection cavities.[2,4-7]

While the benefits of SRS are well recognized, not all patients are candidates for single-fractioned radiosurgery. For large lesions greater than 3 cm in size, the maximal tolerated dose may be inadequate for local control.[8] Additionally, the increased risk for treatment-related toxicity decreases the therapeutic index of single-fractioned SRS. For such lesions, hfSRS treatment delivered in 3 to 5 fractions over multiple days is preferred.

The rationale for hfSRS for brain metastases is due to the relative radiosensitivity of

TABLE 1. Summary of Series Using hfSRS for Treatment of Brain Metastases.

Study	Number of patients/lesions	Fractionation used	Lesion size (median)	Local control	Toxicity
Manning, 2000[11]	32/57	6-12 Gy × 3	2.2 cc	91% crude	3.5% RN
Aoyama, 2003[14]	87/159	8.75 × 4	3.3 cc	81% @ 1 yr	7% grade 3 RN
Lindvall, 2005[18]	47/47	8 Gy × 5	–	84% crude	6.25% RN, 1 pt death
Aoki, 2006[13]	44/65	5-6 Gy × 3-5	–	72% @1 yr	2% grade 3 RN
Naraynana, 2007[19]	20/20	6 Gy × 5	–	70% @ 1 yr	15% RN
Fahrig, 2007[12]	150/228	6-7 Gy × 5 5 Gy × 7 10 Gy × 4	6.1 cc	NR	22% RN 7% RN 0% RN
Giubilei, 2009[16]	30/44	6 Gy × 3 8 Gy × 4	4.8 cc	86% @ 1 yr	NR
Kwon, 2009[17]	27/52	20-35 Gy × 4-6	0.5 cc	68% @ 1 yr	5.8% RN
Ogura, 2012[20]	39/46	7 Gy × 5 WBRT 4-5 Gy ×5	1.8 cm	87% at 1 yr	2.5% grade 3 RN
Wang, 2012[21]	37/37	8 Gy ×3	–	80% at 6 mo	9% RN
DePotter, 2013[15]	35/58	WBRT + 6 Gy × 5	8.6 cc	66% @ 1 yr	11% grade 3 RN
Eaton, 2013[23]	42/42	5-8 Gy × 3-5	13.6 cc	62% @ 1 yr	7% RN
Vogel, 2015[22]	31/26	8 Gy × 3 5-7 Gy × 5	3.8 cm	68.5% @ 1 yr	10% RN
Zhong, 2017[24]	37/37	5-8 Gy × 3-5	–	84% at 1 yr	13.5% grade 2 RN

NR = not reported; RN = radiation necrosis; cc = cubic centimeters.

tumors and surrounding normal structures. The relationship between radiation dose and tumor cell survival has been approximated by the linear quadratic model.[9] Using this model, the biologically effective dose (BED) to the tissue of interest can be approximated using the tissue's α/β ratio, which represents the dose at which the linear and quadratic components of cell kill are equal. Given that the α/β ratio for tumors are generally much higher than that of normal critical structures, the effect of radiation on tumors is relatively less affected by fractionation than normal brain tissues. Thus, hypofractionation preferentially spares normal critical structures while maintaining its therapeutic effect on tumor cells.

Patient Selection and Treatment

The use of single-fraction SRS is typically limited to targets measuring less than 3 to 4 cm in maximal dimension and producing minimal mass effect (less than 1 cm of midline shift), given concerns for greater toxicity with increasing size or treatment-related edema causing significant neurological symptoms or herniation.[8] The maximal tolerated dose for lesions measuring 3 to 4 cm in diameter is 15 Gy based on RTOG 90-05,[3] and though considered acceptable for single-fraction treatment, many authors have reported suboptimal tumor control for these large lesions from single-fractioned SRS, as reviewed by Linskey et al (2009).[8] Furthermore, proximity to critical normal structures such as the optic pathway and brainstem can prevent the use of single-fraction SRS when it is not possible to prevent the critical structure from receiving an unacceptable dose.[10] In these situations, hfSRS is preferred to single-fraction treatment.

Authors have advocated hfSRS treatment using a range of fractionation schedules (Table 1). Manning et al[11] reported using 3 treatments of 6 to 12 Gy per fraction with a median of 9 Gy per fraction over a 5 to 7-dperiod. Fahrig et al[12] reported the largest cohort of 150 patients with 228 metastases using 5 treatments of 6 to 7 Gy, 7 treatments of 5 Gy, and 10 treatments of 4 Gy.[12] Although 7- and 10-treatment fractionations where utilized in that experience, contemporary authors have largely adopted hfSRS regimen with 5 treatments or less.[11,13-22] For the majority of series reported, the most commonly used dosing for 3- and 5-fraction treatments were 8 Gy and 6 to 7 Gy, respectively.[18,19,21-23]

Treatment Outcomes

The reported rates of local control for patients treated with hfSRS are comparable to single-fraction SRS, with 1-yr local control rates ranging from 66% to 91%.[11-16,23] Aoyama et al[14] reported a large series of 87 patients with 159 tumors with a median size of 3.3 cc treated with 4 fractions of 8.75 Gy with a 1-yr local control rate of 81%.[14] Similarly, 6 other studies reported 1-yr local control rates of 80% or higher when fraction sizes of 5 to 8 Gy were used over 3 to 5 fractions.[11,16,18,20,21,24] These authors did not report significant differences in local control between 3- and 5-fraction treatments. These favorable local control rates are especially notable considering the selection bias for larger tumors treated with hfSRS.

In addition to data demonstrating the efficacy of hfSRS, 2 recent prospective trials suggest that single-fraction SRS for large resection cavities may be inadequate. Mahajan et al[6] reported the results of a single-institutional randomized trial evaluating local control in resection cavities treated with single-fraction SRS. In their series, cavities greater than 3.5 cm were randomized to 12 Gy in a single fraction, and this subset demonstrated a 1-yr local control rate of 46%. Similarly, a multi-institutional randomized study also demonstrated lower local control rates in the single-fraction radiosurgery cohort compared with treatment with whole-brain irradiation; the authors

TABLE 2. Summary of Series Using hfSRS for Benign Tumors.

Study	N	Lesion type	Total dose (Gy)/number of fractions	Size/volume	Local control (%)	Complication
Adler, 2006[32]	27	Meningioma	Mean 20.3 Gy/2-5	Mean: 7.7 cc	At 45 mo: 94%	Vision preservation: 94%
Anderson, 2014[39]	37	Acoustic neuroma	20 Gy/5	Median: 0.89 cc	90.5% at 5 yr	2.9% vertigo 2.9% tinnitus
Bria, 2011[33]	73	Meningioma	Median 17.5 Gy/3	Median: 5.54cc	At 1 yr: 95% for WHO grade1	No acute grade 3 1% late grade 3 ataxia
Karam, 2013[34]	37	Acoustic neuroma	25 Gy/5	Median 1.03cc	91% at 3 yr	5% trigeminal paresthesia
Meijer, 2003[35]	80	Acoustic neuroma	20 Gy/4 25 Gy/5	Mean: 2.6 cm	94% at 5 yr	Facial nerve preservation 93%, hearing preservation 75% at 5 yr
Morimoto, 2013[36]	26	Acoustic neuroma	Median: 21 Gy/3	Median: 2.6 cc	95% at 7 yr	Grade 1-2 tinnitus: 3 patients Grade 2 facial nerve disorder: 2 patients Grade 3 hydrocephalus: 1 patient
Puataweepong, 2013[40]	79	Acoustic neuroma	Median: 26 Gy/5	Median: 9.5 cc	95% at 5 yr	<1% hydrocephalus
Song, 1999[37]	31	Acoustic neuroma	25 Gy/5	Mean: 1.1 cc	100% (6-44 mo follow-up)	Trigeminal neuropathy: 2 patients

cc = cubic centimeters.

hypothesized that hfSRS may have yielded higher control rates for large cavities.[2] In contrast, the largest retrospective report of radiosurgery for large resection cavities reported hfSRS treatment with 5 to 8 Gy per fraction in 3 to 5 fractions with 1-yr local control rates of 84% at 1 yr.[24] This series also demonstrated that the local control of large resection cavities was noninferior to those in small cavities when hfSRS was utilized.

Toxicity

The most common significant toxicity associated with cranial radiosurgery is radiation necrosis. In a retrospective comparison of 75 patients with 76 resection cavities, the use of hfSRS was significantly associated with a decreased risk for radiation necrosis compared with single-fractioned SRS.[25] On multivariable analysis, single-fraction SRS demonstrated a hazard ratio of 3.79 (0.83-17.24) compared with hfSRS. Of the reported literature, the rates of grade 2 or higher radiation necrosis range from 7% to 22%,[12,22,24,25] while the rates of grade 3 or higher radiation necrosis range from 2% to 11%.[13-15] Overall, the reported data suggest that proper utilization of hfSRS can achieve radiation necrosis rates comparable to those associated with single-fraction treatment of smaller targets.

BENIGN TUMORS

Radiosurgery has been widely used for the treatment of benign brain tumors including meningiomas[26-29] and acoustic neuromas,[30,31] achieving greater than 90% local control with the utilization of single-fraction SRS. Single-fraction radiosurgery doses for these benign lesions are lower than that utilized for metastatic tumors, typically 12 to 14 Gy for meningiomas and 12 to 13 Gy for acoustic neuromas. However, analogous to the treatment of brain metastases, proximity to critical structures as well as large treatment volume can limit the use of single-fraction SRS. McTyre et al[32] reported favorable toxicity rates with the use of fractionated Gamma Knife radiosurgery (Elekta, Stockholm, Sweden) for the treatment of periotic benign tumors.

Reports of hfSRS for the treatment of meningiomas are relatively limited. Adler et al[33] reported Stanford's experience in 27 patients prescribing an average dose of 20.3 Gy in 2 to 5 fractions to meningiomas within 2 mm of the optic apparatus. The authors reported local control of 94% at a median follow-up of 45 mo.[33] Additionally, these authors reported that 94% of the patients experienced unchanged or improved vision following treatment despite the proximity of the tumors to the optic apparatus. Similarly, Bria et al[34] reported local control rate of 95% at a median follow-up of 16 mo in 73 patients treated to a median dose of 17.5 Gy in 3 fractions. These authors reported a 0% grade 3 or greater acute toxicity and 1 patient with late grade 3 ataxia.

Similar to the treatment of large meningiomas, hfSRS has been preferred in the treatment of large acoustic neuromas when radiosurgery is utilized. In the reported series, authors have utilized 6 to 7 Gy per fraction over 3 fractions as well as 5 Gy per fraction over 5 fractions with local control rates of 91% to 100% after follow-up intervals ranging from 6 mo to 7.3 yr (Table 2).[35-38] Additionally, these studies reported rates of hearing preservation to range from 50% to 81%, and the rates of cranial nerve V and VII loss to be less than 10%, all of which are comparable to those reported for single-fractioned SRS. Meijer et al[36] retrospectively compared 129 patients with acoustic neuromas treated at their institution with 5-fraction hfSRS compared with single-fraction SRS and did not find statistical difference in local control,

facial nerve preservation, or hearing preservation.[36] Additionally, Anderson et al[39] and Puataweepong et al[40] reported similar rates of hearing preservation among patients treated with either single-fraction SRS, hfSRS, or conventionally fractionated radiotherapy at their respective institutions.

Overall, the use of hfSRS for the treatment of benign tumors unsuitable for single-fractioned SRS has demonstrated high rates of local control with tolerable toxicity. However, the follow-up time in the current reports generally tend to be significantly less than those experiences using single-fractioned SRS. In addition to hfSRS, conventionally fractionated radiotherapy with doses of 1.8 to 2.0 Gy daily also remains an option for those benign tumors that are large tumors or in proximity to critical normal structures.

ARTERIOVENOUS MALFORMATIONS

Cerebral AVMs are congenital lesions in which abnormal collections of blood vessels composed of dilated arteries and veins with dysplastic vessels are present without connecting capillary beds. This type of abnormality is rare, found in approximately 0.05% of the population.[41] Although the rates of hemorrhage are typically reported to be 2% to 4% per year when left untreated, individual risks may be as high as 34% annually depending on location, flow, venous drainage, and history of previous hemorrhage.[41–43] While the results of the ARUBA study were controversial regarding treatment of unruptured asymptomatic AVMs,[44] there is consensus on treatment of ruptured AVMs.[41]

Options for definitive treatment for AVMs include microsurgery and radiosurgery, with embolization as an adjunct. The primary objective is complete obliteration of the AVM. Historically, treatment of small AVMs with high-dose single-fraction radiosurgery or surgery has resulted in favorable obliteration rates. However, the treatment of large AVMs remains challenging, as a large portion is considered inoperable, especially those classified as Spetzler–Martin Grade IV or V.[45] Additionally, single-fractioned SRS to such large volumes may result in intolerable toxicities. The optimal selection and treatment of patients with large AVMs with hypofractionated SRS regimen will be discussed below.

Patient Selection

The major indication for hfSRS in the treatment of AVMs is for large, inoperable lesions that require definitive treatment. Most authors agree that definitive treatment is not recommended for patients with minimal to mild symptoms.[44,46] Acceptable indications for treatment include previous hemorrhage and significant neurological symptoms, including seizures and neurological deficits.[46] Although there is no clear consensus on inoperable criteria, many authors consider Spetzler–Martin Grades IIIB-V inoperable.

Currently, there is no consensus on the definition of a "large" AVM. While the Spetzler–Martin classification is commonly utilized, the only size component of this grading system uses maximum diameter stratifications of 3 and 6 cm. Additionally, this grading scale does not correlate with successful AVM radiosurgery, due to its insensitivity to important factors such as AVM volume.[47,48] Assuming a roughly spherical shape, a 2 to 3 cm maximum diameter would correspond to an approximate value of 10 to 14 cc, thus making 10 to 14 cc common thresholds for AVMs to be considered large in radiosurgical literature.[49,50] Pollock and Flickinger[51] proposed a radiosurgery-based scoring system that is derived by AVM volume, patient age, and AVM location and successfully correlates with patient outcomes after single-session radiosurgery.

Dosing Fractionation

Single-fraction SRS is effective in treating small AVMs, with complete obliteration rates of 72% to 96%.[52] However, the dose–volume relationship can be unfavorable for large AVMs when treated in a single fraction, resulting in high complication rates for effective doses.[53-55] hfSRS refers to the treatment of the AVM in multiple fractions also considered a dose-staged SRS, in contrast to volume-staged SRS, in which the AVM is treated by combining multiple full-dose treatments to different parts of the AVM at different times. Volume-staged SRS represents a popular treatment option and has generally been thought to provide higher obliteration rates compared with dose-staged SRS with the sacrifice of a less favorable complication profile.[56] Given that volume-staged SRS is not true hypofractionation, dose-staged SRS will be the focus of this review.

Typically, the target cells for the obliteration of AVMs (ie cells of the nidus) have a small α/β ratio, at 2 to 3 Gy, similar to late-responding normal tissues.[57] As long as the α/β ratio for the AVM is higher than that of the surrounding normal tissue, fractionated treatment will have therapeutic advantages over single-fraction treatment.[58] However, as fractionation increases, the therapeutic ratio for the obliteration of AVMs becomes less favorable. Early attempts at fractionated SRS using fraction sizes of 2 to 4 Gy to a total of 50 Gy in the treatment of large AVMs demonstrated poor obliteration rates of 8% with high rates of complication.[59] These authors concluded that fractionated RT in less than 4 Gy per fraction cannot be recommended. Consequently, modern hfSRS for the treatment of large AVMs delivers doses of >4 Gy per fraction in up to 5 to 6 fractions. Using the derived α/β ratio of 2.2 Gy, Qi et al[57] proposed the fractionation schemes of 7 Gy × 4, 5.6 Gy × 6, 4.7 Gy × 8, and 4.2 Gy × 10. These schemes have an overall biologically equivalent dose for normal neurological tissues ($BED_{2.2}$) roughly equivalent to 63 Gy if delivered in 2 Gy per day conventional fractionation, which is the BED equivalent to a single-fraction treatment of approximately 15 Gy.

Generally, authors have used fractionation schemes of 4 to 7 Gy per fraction, treated over a wide range of 2 to 11 fractions, with a total dose ranging from 24 to 55 Gy (Table 2). Special dosing considerations can be made based on AVM volume and location.[50,60] Typically, no clinical target volume expansion margin is added for uncertainty in target definition, given the vascular lesion typically has a sharp border for target

TABLE 3. Summary of Series Using hfSRS for Large AVMs.

Study	N	Total dose (Gy)/number of fractions	Size/volume	Complete obliteration rate (%)	Complication
Aoyama, 2001[58]	26	24-28. 8 Gy/4	Mean: 2.26 cm	At 3 yr: 53%	Hemorrhage: 12% Radiation necrosis: 0
Lindvall, 2003[60]	29	30-35 Gy/5	Mean: 11.5 cc	At 5 yr: 81% (4-10 mL) 70% (>10 mL)	Hemorrhage: 7% Radiation necrosis: 7%
Veznedaroglu, 2004[50]	24	42 Gy/6 30 Gy/5	Mean: 23.8 cc Mean: 14.5 cc	83% (42 Gy/6) 22% (30 Gy/5)	Hemorrhage: NR Radiation necrosis: 14% (42 Gy/6) 8.7% (30 Gy/5)
Silander, 2004[63,*]	19	20-25 Gy/2 or 4	Mean: 24 cc	36%	Hemorrhage: NR Radiation necrosis: 26%
Chang, 2004[47]	33	20-28/4	Eloquent area or >2.5 cm	At 3 yr: 32% At 5 yr: 61% At 6 yr: 71%	Hemorrhage: 22% Radiation necrosis: 3%
Zabel-du Bois, 2006[61]	15	20-32.5/4-5	Median: 27 cc	At 3 yr: 17% At 4 yr: 33%	Hemorrhage: 20% Radiation necrosis: 0%
Xiao, 2010[46]	20	25-30/5-6	Median: 46.84 cc	0% at median 32 mo	Hemorrhage: 2%/yr Radiation necrosis: NR
Blamek, 2012[62]	49	12-28/2-4	Mean: 25.1 cc	At 1 yr: 7% At 2 yr: 11% At 3 yr: 21%	Hemorrhage: 4% Radiation necrosis: 12%
Chen, 2016[66]	35	28-35/5	Median: 11.43 cc	74%	Hemorrhage: 5% Radiation necrosis: 25%
Bostrom, 2016[38]	14	30-55 Gy/5-11	Mean: 4.77 cc Median: 2.79 cc	28.5%	Hemorrhage: 12% Radiation necrosis: 7%

*proton therapy was utilized; NR = not reported; cc = cubic centimeters.

delineation. The planning target volume expansion margin, which is meant to account for uncertainty in patient positioning, generally should be determined by the reproducibility of the institutional specific irradiation technique. While some authors delivered daily fractions, others have delivered every other day treatment, totaling up to 2 wk.

Obliteration Rates

Several studies have demonstrated an increased probability of obliteration with increased fraction size.[47,50,58,60,61] Veznedarogulu et al[50] found a 7-fold increase in obliteration rates with a fraction size of 7 Gy vs 5 Gy. These findings were supported by several subsequent studies demonstrating obliteration rates of 50% to 83% vs 8% to 22% for doses of 7 Gy vs less than 7 Gy, respectively.[47,58,60] Blamek et al[62] most recently reported similar findings with a trend towards higher obliteration rates in fraction dose ≥8 Gy.

The obliteration rates are listed in Table 3 for reported studies using hfSRS. Aoyama et al[58] demonstrated a 53% (95% confidence interval [CI]: 28-77%) obliteration rate at 3 yr for patients treated with hfSRS, compared with 71% (95% CI: 48-93%) for the single-fraction treatment. The authors reported that the obliteration rates for the hfSRS cohort were not statistically inferior.[58] The authors argue for the absence of inferiority considering hfSRS was used for patients with larger AVMs, or ones in eloquent areas. Silander et al[63] reported similar outcomes with proton therapy, demonstrating a complete obliteration rate of 36% and a partial obliteration rate of 68% at a median of 40 mo of follow-up.[63] The highest obliteration rates were reported by Veznedargolu et al[50] of 83% when 7 Gy per fraction was used. Similarly, Lindvall et al[60] reported excellent 5-yr obliteration rates at 81% for those AVMs < 10 cc, and 70% for those > 10 cc. In general, most authors have reported comparable rates of obliteration through hfSRS compared with single-fractionated SRS, though the data for hfSRS for AVMs is limited in patient number and follow-up when compared to the more extensive volume of data for single-fraction radiosurgery

Complications

The 2 significant complications that may occur following the radiosurgical treatment of AVMs are hemorrhage prior to the time of obliteration and radiation-related imaging changes/necrosis. Several factors may contribute to the rates of postradiosurgery hemorrhage, including rehemorrhage from previously ruptured AVMs and complications from prior embolization or microsurgeries. However, the reported rates of hemorrhage following hfSRS range from 2% to 22%,[46,47,50,58,60,61] summarized in Table 2. Moosa et al[64] reported a pooled analysis of 7 volume-staged hfSRS

series with a combined hemorrhage rate of 17.8% (95% CI: 12.3-23.3%). While these reported rates of hemorrhage may be higher than those reported for single-fraction SRS, there may be significant selection bias given that hfSRS is typically used in larger AVMs or those in eloquent areas.

Radiosurgery for AVMs is also associated with treatment-related T2-MRI changes, which can be asymptomatic or manifest ranging from transient symptoms to symptomatic radiation necrosis.[50,54,58] A pooled analysis of 7 studies utilizing hfSRS demonstrates a combined rate of asymptomatic radiographic changes and symptomatic necrosis in 12.5% of patients.[64] The authors also found that the rates of these treatment-related changes in dose-staged SRS were comparable to volume-staged SRS.[64]

FUTURE DIRECTIONS

While the cited studies show great potential for the use of hfSRS, the data presented by the authors are ultimately retrospective in nature. Thus, the fractionation schemes used have generally been extrapolated, without true dose-escalation data. Currently, the University of Pittsburgh (NCT02054689) and Emory University (NCT01705548) are accruing Phase I studies to investigate the maximum tolerated hypofractionated dose for the treatment of large brain metastases, while a Phase I/II study is being conducted at Stanford University to additionally evaluate disease-related outcomes (NCT00928226). Similarly, a Phase II study is currently accruing at MD Anderson (NCT02798029) to evaluate the efficacy, safety, and cost of hfSRS into the treatment of large brain metastases.[65]

Limitations

This review is based on literature that is largely retrospective in nature and thus may be heavily influenced by selection and publication bias. However, conservative interpretation of the data at hand still allows for meaningful observations to be made.

SUMMARY

Hypofractionated radiosurgery is a viable alternative to single-fraction radiosurgery, especially when the risk of single-fraction treatment is high, and has been successfully utilized for a variety of indications including brain metastases as well as benign tumors and AVMs. In brain metastases, 3 to 5 fractions are commonly used with doses ranging from 6 to 8 Gy per fraction. For meningiomas and acoustic neuromas, 5 fractions of 5 Gy appear efficacious. And in AVMs, fraction sizes of greater than 4 Gy should be used, with increased obliteration rates for 7 Gy or more per fraction. Tumor control and rates of AVM obliteration appear comparable to outcomes observed with single-fraction treatment when hfSRS is utilized appropriately. Additionally, the toxicities of hfSRS appear similar to those seen with single-fraction radiosurgery of smaller lesions.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;10(11):1037-1044.
2. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases. *JAMA*. 2016;316(4):401-409.
3. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys*. 2000;47(2):291-298.
4. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet*. 2004;363(9422):1665-1672.
5. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases. *JAMA*. 2006;295(21):2483-2491.
6. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18(8):1040-1048.
7. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18(8):1049-1060.
8. Linskey ME, Andrews DW, Asher AL, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2010;96(1):45-68.
9. Hall EJ, Giaccia AJ. *Radiobiology for the Radiologist*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2012.
10. Hiniker SM, Modlin LA, Choi CY, et al. Dose-response modeling of the visual pathway tolerance to single-fraction and hypofractionated stereotactic radiosurgery. *Semin Radiat Oncol*. 2016;26(2):97-104.
11. Manning MA, Cardinale RM, Benedict SH, et al. Hypofractionated stereotactic radiotherapy as an alternative to radiosurgery for the treatment of patients with brain metastases. *Int J Radiat Oncol Biol Phys*. 2000;47(3):603-608.
12. Fahrig A, Ganslandt O, Lambrecht U, et al. Hypofractionated Stereotactic Radiotherapy for Brain Metastases. *Strahlenther Onkol*. 2007;183(11):625-630.
13. Aoki M, Abe Y, Hatayama Y, Kondo H, Basaki K. Clinical outcome of hypofractionated conventional conformation radiotherapy for patients with single and no more than three metastatic brain tumors, with noninvasive fixation of the skull without whole brain irradiation. *Int J Radiat Oncol Biol Phys*. 2006;64(2):414-418.
14. Aoyama H, Shirato H, Onimaru R, et al. Hypofractionated stereotactic radiotherapy alone without whole-brain irradiation for patients with solitary and oligo brain metastasis using noninvasive fixation of the skull. *Int J Radiat Oncol Biol Phys*. 2003;56(3):793-800.
15. De Potter B, De Meerleer G, De Neve W, Boterberg T, Speleers B, Ost P. Hypofractionated frameless stereotactic intensity-modulated radiotherapy with whole brain radiotherapy for the treatment of 1-3 brain metastases. *Neurol Sci*. 2013;34(5):647-653.
16. Giubilei C, Ingrosso G, D'Andrea M, Benassi M, Santoni R. Hypofractionated stereotactic radiotherapy in combination with whole brain radiotherapy for brain metastases. *J Neurooncol*. 2009;91(2):207-212.
17. Kwon AK, Dibiase SJ, Wang B, Hughes SL, Milcarek B, Zhu Y. Hypofractionated stereotactic radiotherapy for the treatment of brain metastases. *Cancer*. 2009;115(4):890-898.
18. Lindvall P, Bergstrom P, Lofroth PO, Henriksson R, Bergenheim AT. Hypofractionated conformal stereotactic radiotherapy alone or in combination with whole-brain radiotherapy in patients with cerebral metastases. *Int J Radiat Oncol Biol Phys*. 2005;61(5):1460-1466.
19. Narayana A, Chang J, Yenice K, et al. Hypofractionated stereotactic radiotherapy using intensity-modulated radiotherapy in patients with one or two brain metastases. *Stereotact Funct Neurosurg*. 2007;85(2-3):82-87.

20. Ogura K, Mizowaki T, Ogura M, et al. Outcomes of hypofractionated stereotactic radiotherapy for metastatic brain tumors with high risk factors. *J Neurooncol*. 2012;109(2):425-432.
21. Wang CC, Floyd SR, Chang CH, et al. Cyberknife hypofractionated stereotactic radiosurgery (HSRS) of resection cavity after excision of large cerebral metastasis: efficacy and safety of an 800 cGy x 3 daily fractions regimen. *J Neurooncol*. 2012;106(3):601-610.
22. Vogel J, Ojerholm E, Hollander A, et al. Intracranial control after Cyberknife radiosurgery to the resection bed for large brain metastases. *Radiat Oncol*. 2015;10(1):221.
23. Eaton BR, Gebhardt B, Prabhu R, Shu HK, Curran WJ, Jr, Crocker I. Hypofractionated radiosurgery for intact or resected brain metastases: defining the optimal dose and fractionation. *Radiat Oncol*. 2013;8(1):135.
24. Zhong J, Ferris MJ, Switchenko J, et al. Postoperative stereotactic radiosurgery for resected brain metastases: a comparison of outcomes for large resection cavities. *Pract Radiat Oncol*. 2017;7(6):e419-e425
25. Eaton BR, LaRiviere MJ, Kim S, et al. Hypofractionated radiosurgery has a better safety profile than single fraction radiosurgery for large resected brain metastases. *J Neurooncol*. 2015;123(1):103-111.
26. Mansouri A, Guha D, Klironomos G, Larjani S, Zadeh G, Kondziolka D. Stereotactic Radiosurgery for Intracranial Meningiomas. *Neurosurgery*. 2015;76(4):362-371.
27. Flannery TJ, Kano H, Lunsford LD, et al. Long-term control of petroclival meningiomas through radiosurgery. *J Neurosurg*. 2010;112(5):957-964.
28. Lee JY, Niranjan A, McInerney J, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery providing long-term tumor control of cavernous sinus meningiomas. *J Neurosurg*. 2002;97(1):65-72.
29. Sheehan JP, Starke RM, Kano H, et al. Gamma Knife radiosurgery for sellar and parasellar meningiomas: a multicenter study. *J Neurosurg*. 2014;120(6):1268-1277.
30. Kondziolka D, Lunsford LD, McLaughlin MR, Flickinger JC. Long-term outcomes after radiosurgery for acoustic neuromas. *N Engl J Med*. 1998;339(20):1426-1433.
31. Murphy ES, Suh JH. Radiotherapy for vestibular schwannomas: a critical review. *Int J Radiat Oncol Biol Phys*. 2011;79(4):985-997.
32. McTyre E, Helis CA, Farris M, et al. Emerging Indications for Fractionated Gamma Knife Radiosurgery. *Neurosurgery*. 2017;80(2):210-216.
33. Adler JR, Jr, Gibbs IC, Puataweepong P, Chang SD. Visual field preservation after multisession cyberknife radiosurgery for perioptic lesions. *Neurosurgery*. 2008;62(Suppl 2):733-743.
34. Bria C, Wegner RE, Clump DA, et al. Fractionated stereotactic radiosurgery for the treatment of meningiomas. *J Cancer Res Ther*. 2011;7(1):52-57.
35. Karam SD, Tai A, Strohl A, et al. Frameless fractionated stereotactic radiosurgery for vestibular schwannomas: a single-institution experience. *Front Oncol*. 2013;3:121, doi: 10.3389/fonc.2013.00121.
36. Meijer OW, Vandertop WP, Baayen JC, Slotman BJ. Single-fraction vs. fractionated linac-based stereotactic radiosurgery for vestibular schwannoma: a single-institution study. *Int J Radiat Oncol Biol Phys*. 2003;56(5):1390-1396.
37. Morimoto M, Yoshioka Y, Kotsuma T, et al. Hypofractionated stereotactic radiation therapy in three to five fractions for vestibular schwannoma. *Jpn J Clin Oncol*. 2013;43(8):805-812.
38. Song DY, Williams JA. Fractionated stereotactic radiosurgery for treatment of acoustic neuromas. *Stereotact Funct Neurosurg*. 1999;73(1-4):45-49.
39. Anderson BM, Khuntia D, Bentzen SM, et al. Single institution experience treating 104 vestibular schwannomas with fractionated stereotactic radiation therapy or stereotactic radiosurgery. *J Neurooncol*. 2014;116(1):187-193.
40. Puataweepong P, Dhanachai M, Dangprasert S, et al. Linac-based stereotactic radiosurgery and fractionated stereotactic radiotherapy for vestibular schwannomas: comparative observations of 139 patients treated at a single institution. *J Radiat Res*. 2014;55(2):351-358.
41. Bostrom JP, Bruckermann R, Pintea B, Bostrom A, Surber G, Hamm K. Treatment of cerebral arteriovenous malformations with radiosurgery or hypofractionated stereotactic radiotherapy in a consecutive pooled linear accelerator series. *World Neurosurg*. 2016;94:328-338.
42. Brown RD, Jr, Wiebers DO, Forbes G, et al. The natural history of unruptured intracranial arteriovenous malformations. *J Neurosurg*. 1988;68(3):352-357.
43. Stapf C, Mast H, Sciacca RR, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. *Neurology*. 2006;66(9):1350-1355.
44. Mohr JP, Parides MK, Stapf C, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet North Am Ed*. 2014;383(9917):614-621.
45. Speizler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg*. 2008;108(1):186-193.
46. Xiao F, Gorgulho AA, Lin CS, et al. Treatment of giant cerebral arteriovenous malformation: hypofractionated stereotactic radiation as the first stage. *Neurosurgery*. 2010;67(5):1253-1259.
47. Chang SD, Marcellus ML, Marks MP, Levy RP, Do HM, Steinberg GK. Multimodality treatment of giant intracranial arteriovenous malformations. *Neurosurgery*. 2007;61(1 Suppl):432-442.
48. Zhao J, Yu T, Wang S, Zhao Y, Yang WY. Surgical treatment of giant intracranial arteriovenous malformations. *Neurosurgery*. 2010;67(5):1359-1370.
49. Miyawaki L, Dowd C, Wara W, et al. Five year results of LINAC radiosurgery for arteriovenous malformations: outcome for large AVMS. *Int J Radiat Oncol Biol Phys*. 1999;44(5):1089-1106.
50. Veznedaroglu E, Andrews DW, Benitez RP, et al. Fractionated stereotactic radiotherapy for the treatment of large arteriovenous malformations with or without previous partial embolization. *Neurosurgery*. 2008;62(Suppl 2):763-775.
51. Pollock BE, Flickinger JC. A proposed radiosurgery-based grading system for arteriovenous malformations. *J Neurosurg*. 2002;96(1):79-85.
52. Jones J, Jang S, Getch CC, Kepka AG, Marymont MH. Advances in the radiosurgical treatment of large inoperable arteriovenous malformations. *Neurosurg Focus*. 2007;23(6):E7.
53. Flickinger JC, Kondziolka D, Maitz AH, Lunsford LD. An analysis of the dose-response for arteriovenous malformation radiosurgery and other factors affecting obliteration. *Radiother Oncol*. 2002;63(3):347-354.
54. Flickinger JC, Pollock BE, Kondziolka D, Lunsford LD. A dose-response analysis of arteriovenous malformation obliteration after radiosurgery. *Int J Radiat Oncol Biol Phys*. 1996;36(4):873-879.
55. Pan DH, Guo WY, Chung WY, Shiau CY, Chang YC, Wang LW. Gamma knife radiosurgery as a single treatment modality for large cerebral arteriovenous malformations. *J Neurosurg*. 2000;93(Suppl 3):113-119.
56. Ilyas A, Chen CJ, Ding D, et al. Cyst formation after stereotactic radiosurgery for brain arteriovenous malformations: a systematic review. *J Neurosurg*. 2017;26:1-10.
57. Qi XS, Schultz CJ, Li XA. Possible fractionated regimens for image-guided intensity-modulated radiation therapy of large arteriovenous malformations. *Phys Med Biol*. 2007;52(18):5667-5682.
58. Aoyama H, Shirato H, Nishioka T, et al. Treatment outcome of single or hypofractionated single-isocentric stereotactic irradiation (STI) using a linear accelerator for intracranial arteriovenous malformation. *Radiother Oncol*. 2001;59(3):323-328.
59. Karlsson B, Lindqvist M, Blomgren H, et al. Long-term results after fractionated radiation therapy for large brain arteriovenous malformations. *Neurosurgery*. 2005;57(1):42-49.
60. Lindvall P, Bergstrom P, Lofroth PO, et al. Hypofractionated conformal stereotactic radiotherapy for arteriovenous malformations. *Neurosurgery*. 2003;53(5):1036-1043.
61. Zabel-du Bois A, Milker-Zabel S, Huber P, Schlegel W, Debus J. Linac-based radiosurgery or hypofractionated stereotactic radiotherapy in the treatment of large cerebral arteriovenous malformations. *Int J Radiat Oncol Biol Phys*. 2006;64(4):1049-1054.
62. Blamek S, Larysz D, Miszczyk L, Idasiak A, Rudnik A, Tarnawski R. Hypofractionated stereotactic radiotherapy for large or involving critical organs cerebral arteriovenous malformations. *Radiol Oncol*. 2013;47(1):50-56.
63. Silander H, Pellettieri L, Enblad P, et al. Fractionated, stereotactic proton beam treatment of cerebral arteriovenous malformations. *Acta Neurol Scand*. 2004;109(2):85-90.
64. Moosa S, Chen CJ, Ding D, et al. Volume-staged versus dose-staged radiosurgery outcomes for large intracranial arteriovenous malformations. *Neurosurg Focus*. 2014;37(3):E18.
65. NIH. US National Library of Medicine. https://clinicaltrials.gov/. 2017.
66. Chen JC, Mariscal L, Girvigian MR, et al. Hypofractionated stereotactic radiosurgery for treatment of cerebral arteriovenous malformations: outcome analysis with use of the modified arteriovenous malformation scoring system. *J Clin Neurosci*. 2016;29:155-161.

COMMENT

The authors present a comprehensive review on the use of hypofractionated radiotherapy as a treatment option for brain metastases, benign brain tumors, and AVM. This modality continues to evolve as a means of increasing the therapeutic ratio in scenarios where single fraction radiosurgery may be limited by toxicity concerns. In cases of larger tumors, tumors with close proximity to optic structures, hearing preservation of vestibular schwannomas and re-irradiation of previously treated tumors, hypofractionation is carving a clear role in the available armamentarium to radiation oncologists and neurosurgeons. The ability to perform hypofractionated treatments is also becoming increasingly common in the community setting, increasing access to patients for treatments that are non-invasive, and potentially less toxic than large-field conventionally fractionated radiotherapeutic approaches. There is still need for caution with regards to dosing and toxicity limits as the data for hypofractionation is not as mature as it is for single fraction radiosurgery. Late toxicities of treatment can occur years after the initial treatment, and as such, long-term toxicity data is not yet available. Moving forward, future prospective studies will need to integrate the usage of hypofractionation as a viable treatment alternative.

Michael D. Chan
Winston-Salem, North Carolina