Stereotactic Radiosurgery for Intracranial Meningiomas: Current Concepts and Future Perspectives

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Meningiomas are among the most common adult brain tumors. Although the optimal management of meningiomas would provide complete elimination of the lesion, this cannot always be accomplished safely through resection. Therefore, other therapeutic modalities, such as stereotactic radiosurgery (as primary or adjunctive therapy), have emerged. In the current review, we have provided an overview of the historical outcomes of various radiosurgical modalities applied in the management of meningiomas. Furthermore, we provide a discussion on key factors (eg World Health Organization grade, lesion size, and lesion location) that affect tumor control and adverse event rates. We discuss recent changes in our understanding of meningiomas, based on molecular and genetic markers, and how these will change our perspective on the management of meningiomas. We conclude by outlining the areas in which knowledge gaps persist and provide suggestions as to how these can be addressed.

KEY WORDS: Management, Meningioma, Outcome, Radiosurgery, Review

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Meningiomas are common adult brain tumors that originate from the meningeal coverings.[1] Patients with neurofibromatosis type 2 (NF2) and most other patients with spontaneous meningiomas are typically found to have mutations on chromosome 22; however, other chromosomal aberrations (1p, 6q, 10, and 18q) have also been noted.[2] Environmental factors such as ionizing radiation have been established as a causative factor as well.

Although the optimal management of most meningiomas is complete tumor elimination, which is usually achieved through resection, including resection of associated dura and bone (Simpson grade I),[3] not all are amenable to safe surgical resection; thus, other options, such as stereotactic radiosurgery (SRS) or fractionated radiotherapy (FSRT), are advocated for in some patients. Meningiomas are suitable for SRS, either as adjuvant or primary therapy, given their usual regular lesion borders and minimal to no brain invasion.[4]

Here, we provide a review of the literature on the use of SRS in the management of meningiomas, summarizing SRS outcomes, and describing factors predictive of control rates and adverse events. Further, we outline some of the considerations for treatment planning with a particular focus on emerging concepts in the field. We conclude by exploring areas of further research that may potentially change the landscape of SRS as it is currently practiced.

ABBREVIATIONS: ARE, adverse radiation event; **CI,** conformity index; **FSRT,** fractionated radiotherapy; **GK,** Gamma Knife; **GTR,** gross total resection; **HGM,** high-grade meningioma; **LINAC,** linear accelerator; **NF2,** neurofibromatosis type 2; **OA,** optic apparatus; **OS,** overall survival; **PFS,** progression-free survival; **SRS,** stereotactic radiosurgery; **STR,** subtotal resection; **TC,** tumor control; **VS,** vestibular schwannoma; **WHO,** World Health Organization

STEREOTACTIC RADIOSURGERY

The main SRS modalities at most centers are linear accelerators (LINACs) or Gamma Knife (GK) units; both are suitable for SRS administration to a variety of targets, including tumors such as vestibular schwannomas (VS), meningiomas, cerebral metastases, malignant gliomas, and arteriovenous malformations.[5-7] Cyberknife-based LINAC is an SRS technique that incorporates intraoperative imaging.[8] In comparison with LINAC,

GK generates photons from radioactive ^{60}CO.[9] In addition to multiple isocenters, beam blocking and variable collimation is also used to aid in the creation of the 3-dimensional volumes to conform to the target shape.

OUTCOMES FOR MENINGIOMAS TREATED WITH SRS

Initially used for the management of skull base meningiomas that were difficult to resect, SRS has emerged as a valuable modality in the management of meningiomas in other locations as well, demonstrating acceptable tumor control (TC) with a low side-effect profile.[10]

Primary SRS provides TC rates equivalent to a Simpson grade I resection for small- and medium-sized meningiomas (≤3.5 cm diameter) over long-term follow-up.[3,11,12] Adjuvant SRS is beneficial as well, allowing for improved progression-free survival (PFS); Condra et al[13] showed that adjuvant radiosurgery after subtotal resection (STR) resulted in a superior 15-year PFS, compared with patients with gross total resection (GTR) without SRS.

Studies reporting on GK or LINAC outcomes, with a mean/median follow-up of at least 5 years, have demonstrated TC rates varying from 86% to 97% and 89% to 96%, respectively.[14-16] Overall, there is less literature with ≥10 years of follow-up. Outcome reports based on cyberknife devices are limited: Colombo et al[17] reported a 96.3% TC rate and an adverse radiation event (ARE) rate of 3.7% over a 2 year follow-up period. Although these numbers are promising, long-term outcomes are necessary to establish efficacy.

The results of SRS primarily depend on World Health Organization (WHO) grade, lesion location, and lesion diameter/volume. Other factors reported to affect outcomes include age, genetic and molecular markers (eg, vascular endothelial growth factor [VEGF]), and timing of SRS with respect to initial surgical resection.

SRS Outcomes and WHO Grade

Meningioma grade has implications for treatment, with grade I lesions demonstrating the best outcomes (Table 1).[12,18-22] In one of the earliest long-term studies on SRS (primary/adjuvant) for WHO I meningiomas, a 10-year local TC rate of 91% was observed; lesions with largest average diameter >3.5 cm, those with atypical features on imaging, and those with symptoms secondary to mass effect had been excluded.[12] The actuarial TC rates at 5, 10, and 15 years were 97%, 87.2%, and 87.2%, respectively. Other recent shorter-term studies assessing WHO grade I meningiomas in various brain locations have found

TABLE 1. Tumor Control Rate, PFS, OS, and ARE Following SRS for Meningiomas, Stratified by WHO Grade[a]

Author	Year	Device	No. of Patients	Median Follow-up, mo	WHO Grade	Tumor Control Rate, %	2-y/5-y PFS, %	10-y PFS, %	5-y OS, %	10-y OS, %	ARE, %
Bledsoe[18]	2010	GK	116	70.1	I	95.7	99/92	—	98	—	23
DiBiase[21]	2004	GK	162	54	I	91.7	90/86.2	62.5	91	79	8.3
El-Khatib[28]	2011	LINAC	8	60.4	II	85.7	88/75	75	87.5	87.5	3.5
			8		III	57.1	57/57	43			
Eustacchio[19]	2002	GK	121	88.7	I	98.3	—/—	—	—	—	1.7
Flannery[23]	2010	GK	163	72	I	90.0	—/93	90	96	81	8.0
Harris[31]	2003	GK	18	45.6	II	—	98/83	41	59	59	3.3
			12		III	—	84/72	0	59	0	
Kim[27]	2012	GK	25	33	II	56.7	53/—	—	65	—	6.7
			10		III	21.0	10/—	—		—	
Kondziolka[22]	2009	GK	32	31	I	96.9	86.1/—	—	96.9	—	9.6
			15	41	II	50.0		—	85.7	—	
			6	47	III	0.0		—	33.3	—	
Kondziolka[12]	2008	GK	384	48	I	93.0	—/97	87.2	98.9	96.2	7.7
			54	24	II	50.0	75/34	—	74	52	
			29	15	III	17.2	46/10	—	20	0	
Kreil[20]	2005	GK	200	94.8	I	98.0	98.5/98.5	97.2	—	—	2.5
Nicolato[45]	2002	GK	122	48.9	I	97.5	97.5/96.5	—	100	—	4.0
Ojemann[32]	2000	GK	22	24.5	III	—	32/26	—	40	—	23.0
Shin[15]	2001	GK	40	42	All	—	97.5/86.4	82.3	—	—	22.5
Stafford[30]	2001	GK	168	47	I	91.0	100/93	—	100	—	13
			13		II		90/68	—	76	—	
			9		III		25/0	—	0	—	
Zada[64]	2010	GK	116	75	I	94.1	100/98.9	84	—	—	8

[a]ARE, adverse radiation event (permanent symptomatic complication following radiosurgery); GK, gamma knife; LINAC, linear accelerator; OS, overall survival (studies assessing OS often more specifically refer to disease-specific survival); PFS, progression-free survival; WHO, World Health Organization.

similar TC rates in addition to favorable PFS and overall survival (OS) values.[12,21,23-25]

Patients with high-grade meningiomas (HGMs) referred for SRS have often undergone at least 1 surgical resection in addition to possibly a course of FSRT,[26] which limits the subsequent maximal safe SRS dose. Thus, combined with the possibility of acquired radioresistance, success rates for SRS in the management of HGMs are, in general, lower.[12,22,23,26-32] Most studies have reported on patients with an average follow-up period of 2 to 5 years; few studies have demonstrated 10-year follow-up data.[28,31]

El-Khatib et al,[28] using LINAC on 14 patients with grade II and 14 patients with WHO grade III meningiomas (maximal diameter <3 cm), demonstrated 5- and 10-year actuarial TC rates of 81% (grade II) and 60% (grade III). The mean follow-up was 5 years; only few had been followed to 10 years. All patients had undergone a previous microsurgical resection. This study was limited by its small sample size.

Disease-specific survival for patients with HGMs is also low: The OS following SRS for grade II and III patients has been reported to vary from 59% to 81%[28-31,33] and 0% to 59%, respectively.[28-32] In a study by Harris et al[31], which demonstrated improved OS and PFS, the majority of the lesions were within the CS.

Aggressive surgical resection of HGMs may result in a slightly improved PFS and OS.[31,32] However, surgical morbidity can be high, adversely affecting quality of life.[34] Nonetheless, given their poor outcomes, safe surgical resection followed by adjuvant radiosurgery ±FSRT should be attempted whenever possible. Depending on the overall health status of the patient, upfront SRS for the management of small residuals, as opposed to observation, is likely to yield better results, because these lesions have demonstrated the high propensity for recurrence.

Many of the studies assessing TC rates based on WHO grade have either been conducted before the most recent changes in the WHO classification of tumors or have included a combination of lesions before and after reclassification.[35] Therefore, future studies will need to reassess updated TC rates. These would need to consider novel histological and molecular markers (discussed below) that help predict lesion behavior as well.

SRS Outcomes and Location

The origin of meningiomas is typically classified as either skull base or other nonbasal locations (posterior fossa, convexity, parasagittal, parafalcine). Complete microsurgical resection of some skull base tumors is associated with significant risk with a combined morbidity and mortality as high as 67% in specific studies.[36-40] In addition, long-term PFS rates are limited when microsurgical resection is the sole modality utilized, particularly if GTR is not attained, with 30% to 40% recurrence rates in 5- and 10-year follow-up.[41,42] Other intracranial regions, such as the convexity and the CS, are also prone to higher surgical risk, with mortality and permanent morbidity ranging from 10% to 29%, depending on the specific study.[37,43,44] Consequently, particularly when GTR is not safe, SRS is often considered as the primary approach or adjuvant therapy following planned STR. The outcomes following SRS, however, differ based on lesion location (Table 2).[15,28,45-53]

Meningiomas originating from the CS have been shown to respond well to SRS. For these, size is important: Maruyama et al[54]

TABLE 2. Tumor Control Rate, PFS, and ARE Rate Following SRS for Meningiomas Based on Location[a]

Author	Year	Device Used	No. of Patients	Median Follow-up, mo	Location	Tumor Control Rate, %	2-y/5-y PFS, %	10-y PFS, %	5-y OS, %	10-y OS, %	ARE, %
Chuang[48]	2004	LINAC	43	74.5	SB	93.0	—/89.7	—	80.2	—	11.6
Davidson[14]	2007	GK	36	81	SB	97.2	100/100	94.7	100	—	2.8
de Salles[49]	2001	LINAC	40	30	CS	75.8	—/—	—	—	—	7.5
Eustacchio[19]	2002	GK	121	88.7	SB	98.3	−/−	—	—	—	1.7
Flannery[23]	2010	GK	163	72	SB	90.0	—/93	90	96	81	8.0
Han[50]	2008	GK	98	77	SB	90.4	96.8/90.2	—	—	—	17.3
Kondziolka[22]	2009	GK	115	31	SUP	84.3	86.1/71.6	—	86.9	—	9.6
Maruyama[54]	2004	GK	40	47	CS	95.0	—/94.1	—	100	—	12.5
Morita[68]	1999	GK	88	35	SB	97.7	100/95	—	—	—	12.5
Shin[15]	2001	GK	40	42	CS	—	97.5/86.4	82.3	—	—	22.5
Skeie[4]	2010	GK	100	82	CS	84.0	94.2/89.4	83.8	91	—	6.0
Spiegelmann[52]	2002	LINAC	42	36	CS	97.5	97.5/97.5	—	—	—	14.3
Starke[16]	2012	GK	255	78	SB	86.0	99/96	79	—	—	9.8
Zachenhofer[53]	2006	GK	36	103	SB	93.9	97.2/93.9	—	97.2	—	8.0

[a]ARE, adverse radiation event (permanent symptomatic complication following radiosurgery); CS, cavernous sinus; GK, gamma knife; LINAC, linear accelerator; OS, overall survival (studies assessing OS often more specifically refer to disease-specific survival); PC, petroclival; PFS, progression-free survival; SB, skull base (2 or more of cavernous sinus, petroclival, cerebellopontine angle, tentorial, sellar/suprasellar, sphenoidal, optic canal, olfactory groove, foramen magnum); SUP, superficial (convexity, parasagittal).

and Kondziolka et al[55] have suggested that CS tumors <3 cm in maximal diameter are the most appropriate for SRS. This size typically allows an effective dose to be delivered while maintaining visual safety. In addition to taking size into consideration, Maruyama et al[54] have devised a management algorithm whereby microsurgical resection, in most cases planned STR, is recommended for lesions posing a structural risk to the optic apparatus or if diagnosis is unclear. In this suggested approach, the residual is managed with SRS. The greatest challenge in the management of CS meningiomas with SRS is attributed to difficulties in accurately differentiating the target volume from surrounding structures, for contouring purposes, and in determining the safety dose limit tolerated by critical structures.

Although convexity meningiomas are not as intricately associated with critical neural structures such as the cranial nerves and the brainstem, their resection can be high risk regardless, owing to the association of these tumors with venous sinuses, veins, and underlying cortex. Furthermore, resection may be inappropriate for elderly or frail patients.[55] Although reasonable results have been achieved through SRS for convexity meningiomas, the control rates are lower and ARE rates are higher than other locations (Table 2).[22] This is likely multifactorial. A greater proportion of these cases often represent failed resections or recurrences of HGMs referred for SRS; a nonbasal location and a prior resection have been suggested as predictors of HGMs.[56] Others have suggested that convexity meningiomas by nature tend to be of higher grade than meningiomas in other locations, regardless of prior treatment.[57,58] Given the higher tolerability of some cortical brain regions against mass effect—in comparison with the brainstem, for example—it is also likely that patients with convexity meningiomas present later and have larger lesions. The greater pial contact interface also increases the risk of edema following SRS.[10] This holds particularly true if peritumoral edema is present before radiosurgery. Regardless, SRS has a critical role in the management of convexity lesions, particularly as an adjunct in the management of HGMs or recurrences.

Outcomes of SRS and Tumor Size

Tumor size (volume/diameter) affects PFS and OS in patients undergoing SRS for various pathologies, including meningiomas.[32,59-61] Various cutoffs correlating with TC rates and PFS have been suggested.[21,32,55] Lesion size affects the maximal safe deliverable SRS dose, which varies with location; the dose reduction necessary to avoid AREs is the primary limiting factor affecting SRS outcomes for large meningiomas.[55] Although the size categories are a useful guide, predictors of tumor response are multifactorial and binary cutoffs should not be used in isolation.

The Application of SRS in NF2 Patients With Meningiomas

Meningiomas in the setting of NF2 represent a management challenge due to their multiplicity and often young age of patient presentation; therefore, the additive morbidity of any treatment modality on the overall quality of life must be considered. Most NF2 patients harbor meningiomas in locations that are relatively accessible for microsurgery; however, their multiplicity and invasiveness occasionally hinders a safe GTR. While numerous studies have reported on SRS outcomes and hearing preservation for VS in NF2 patients, studies specifically assessing meningiomas are deficient.[60] Extrapolating from VS results, it is likely that SRS is a relatively effective and safer option than attempted GTR for patients with meningiomas in NF2 and should be a key component of the treatment strategy.

ADVERSE EVENTS FOLLOWING SRS

Long-term AREs such as radiation injury, cranial nerve dysfunction, hydrocephalus, vascular occlusion, and peri-tumoral edema are important limiting factors for SRS. Similar to TC rates with SRS, an association between AREs and WHO grade, tumor location, and volume has been well documented. The difficulty with determining true ARE rates is secondary to heterogeneity in ARE definition, ability to decipher from tumor progression, population heterogeneity, and follow-up length. Consequently, wide-ranging AREs have been reported (Tables 1 and 2).

The general range of long-term serious AREs for all meningiomas, independent of grade or location, are quoted as 3% to 43%, depending on the specific study cohort.[15,22,28,30,45,46,55,62-64] Most studies, however, report ARE rates ≤10%. In a recent long-term study by Kondziolka et al,[55] a 10-year morbidity of 7.7% was observed for all meningiomas managed by SRS (primary/adjuvant) over 18 years.

In CS meningiomas, ARE rates vary from 3% to 12%, depending on the particular study.[4,15,45,46,65] Injury to the cranial nerve, particularly the optic apparatus (OA), while uncommon, is the most common concern. While a maximal allowed dose of ≤8 to 10 Gy to the OA is generally accepted, higher doses (≤12 Gy) have been attempted.[55,66-68] The minimum distance of lesion margin and OA (2 mm vs 5 mm) has been debated as well.[69] Advances in imaging and planning software have been paramount in addressing these limits. Figure demonstrate examples of their contribution to the creation of complex dose plans.

Studies with higher ARE profiles have tended to include more HGMs or nonbasal meningiomas[27,62,70] (Tables 1 and 2). The development/worsening of edema, attributed to the release of VEGF or other cytokines, is a major contributor to post-SRS AREs.[62] Tumor location (particularly convexity or parasagittal), tumor volume, radiation dosing, and, in some reports, tumor subtype, can increase the risk of edema. Other factors, such as venous sinus infiltration/occlusion by tumor tissue, have also been identified.[71] The higher rate of edema observed for parasagittal and other nonbasal tumors can be attributed to the higher volume of brain parenchyma radiated, proximity to venous sinuses, and the derivation of blood supply from both dura and pia.[43,63,64,72]

Although other therapies have been attempted, the management of symptomatic edema has traditionally been through

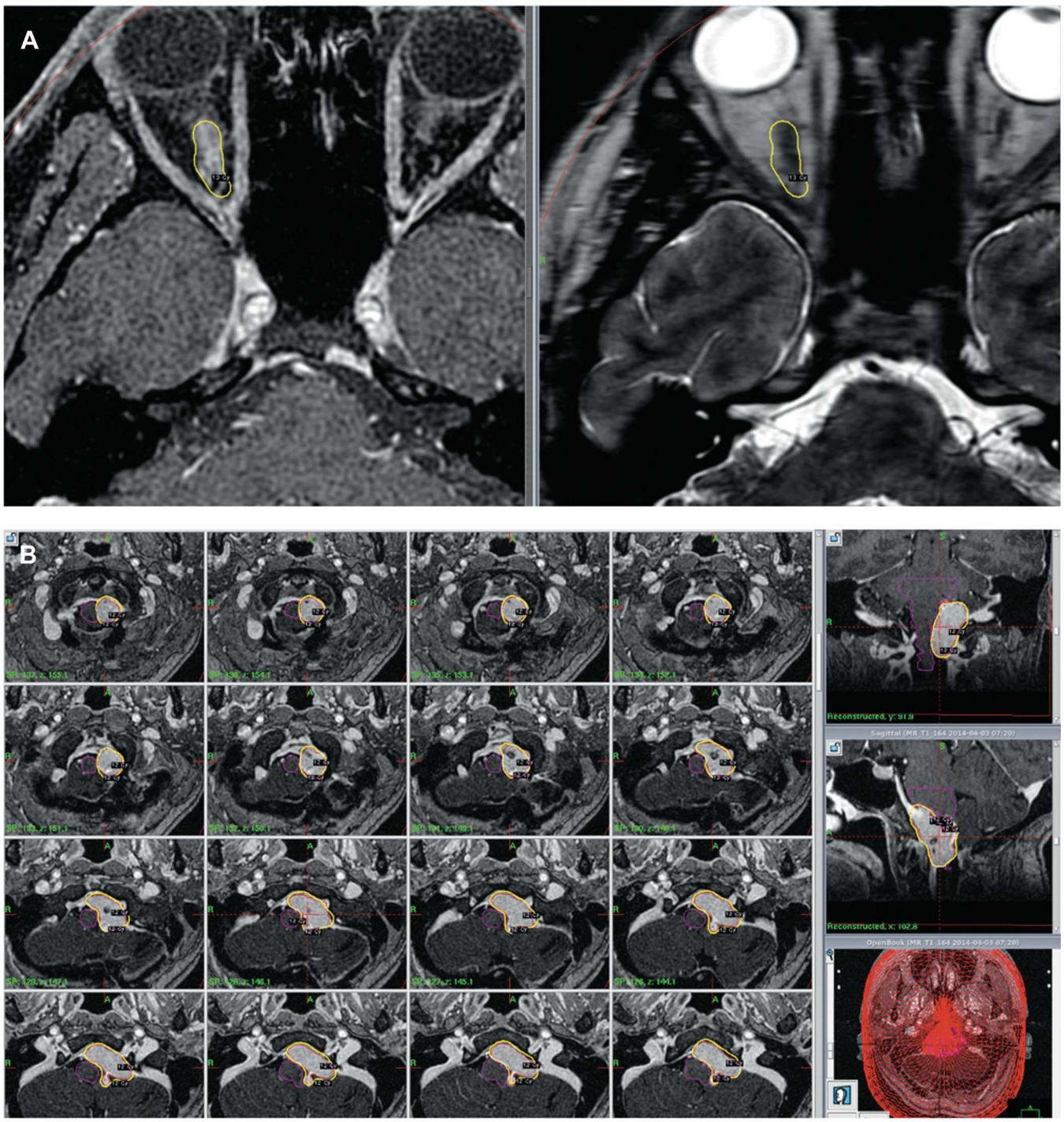

FIGURE. A. *Gamma knife radiosurgery dose plan shown on axial MRI (T1 and T2) in a patient who had lost vision in the right eye from an optic nerve sheath meningioma.* **B**. *Gamma knife radiosurgery dose plan for a recurrent foramen magnum and inferior petrous bone meningioma after prior partial resection. A tumor margin dose of 12 Gy was delivered. Multiple small beam isocenters were used for this complex tumor volume.*

corticosteroids, although these do not directly target VEGF.[22,73] In addition, the optimal corticosteroid-dosing regimen for post-SRS edema has not been established. Therefore, an approach directly targeting the mechanism of action through anti-VEGF agents, such as bevacizumab, may be a consideration.[74]

CLINICAL CONSIDERATIONS AND FUTURE DIRECTIONS

The current review has highlighted current achievements. With advances in genetics and molecular biology, our understanding of the disease and how it should be managed is evolving. Future pertinent topics of investigation include the following: Do SRS indications and the role of observation need to be revisited? How does the biological difference of meningiomas in different locations affect management? What will be the role of the genetics and biology of meningiomas? How can AREs be better differentiated from tumor progression and how can we improve ARE rates? Can we improve outcomes in NF2?

Evolving Indications for SRS and the Role of Observation

Previous studies have developed guidelines for the role of SRS vs observation in the management of grade I and III meningiomas following GTR/STR[31]; regarding grade II meningiomas, however, no clear guidelines are available.[75,76] Although most agree that some form of radiotherapy should be provided following STR, others favor salvage radiotherapy instead, sparing potential upfront AREs.[31,35,77] Given the improved stratification of tumor behavior based on MIB-1 and mitotic activity,[31] it is conceivable that the optimal management strategy—for example, SRS vs observation following GTR—will evolve to incorporate these markers.

Studies have suggested that basal meningiomas have a lower MIB-1 index compared with convexity meningiomas and, therefore, are less aggressive.[78] This potential difference in natural history should be considered when deciding upon observation—in asymptomatic basal meningiomas, for example—as opposed to upfront SRS $\pm$ microsurgery for asymptomatic convexity meningiomas.[78,79] Imaging follow-up, assessing factors such as growth rate, edema, and T2 hyperintensity on MRI would be important considerations.[77,78]

ARE vs Tumor Progression

One of the difficulties associated with determining treatment success following SRS is related to deciphering radiation injury from tumor progression. Numerous suggested imaging strategies include the ratio of nodule size on T2 MRI to total enhancing volume on T1 (lesion quotient),[80] qualitative correlation of T1 and T2 margins (assessment of mismatch),[81] Fluorodeoxyglucose-positron emission tomography, MR spectroscopy, and assessment of cerebral blood volume.[82] Many of these methods have only been tested in cases of brain metastases. A comprehensive solution is hampered by the limited correlation of most imaging studies with histologically confirmed diagnoses. Studies supplemented by histology have been limited by a small sample size. Future long-term, multicentric studies can be helpful.

Strategies to Reduce AREs

Essential to reducing AREs are strategies that enable a reduction of the dose delivered to healthy tissues among which the special sensory nerves and the brainstem may be the most sensitive. Considerations include adjustments to dosimetric parameters of the SRS plan, deescalation of total SRS dose, and/or incorporation of other radiation-based strategies. Some of these considerations have been summarized in Table 3.

In a case-control study assessing dosimetric predictors of toxicity, an increase in the 12 Gy volume of the brainstem was found as a predictor of auditory and motor dysfunction, while a greater number of isocenters near the optic apparatus predicted visual dysfunction.[83] Among plans with an acceptable conformity index (CI) and heterogeneity index, a lower gradient index correlated with higher rates of auditory and motor dysfunction. CI alone was not a predictor of toxicity. Thus, the authors recommended against increasing the number of isocenters to achieve more conformal plans. Overall, plans with CI $\leq$2.0, heterogeneity index $\leq$2.0, and lower gradient index $\geq$3.0 were considered optimal for reducing AREs. However, a lower CI has been associated with a decreased PFS.[84] The association of CI with PFS and AREs is thus clearly a factor that must be taken into consideration. This issue applies to the debate on the "dural tail" as well. While some recommend incorporating it to increase TC rate,[21] others suggest that it may represent hyperemic tissue rather than tumor cells.[77] This is particularly relevant given that alterations to incorporate the tail decrease the overall conformity. We target the dural tail where it appears nodular rather than simply thickened.

Similar to the case of VS, the deescalation of total SRS dose has been considered for meningiomas as well. However, an assessment of patients with mixed WHO grade meningiomas has demonstrated greater TC with median marginal doses $\geq$12 Gy.[57] Further, for HGMs, median marginal doses $\geq$14 Gy have been recommended by some and $\geq$16 Gy by others.[84] Kano has suggested doses $\geq$20 Gy to be associated with a better PFS for recurrent HGMs.[58] Together, these suggest that a dose deescalation to reduce AREs while maintaining high TC rates may be challenging.

This challenge has prompted the exploration of alternative radiation-based modalities for situations where single-session SRS may not be appropriate. Optic nerve sheath meningiomas, for example, are generally better managed with methods such as FSRT, rather than single-session SRS, if preservation of vision is the goal; if vision is already lost, the latter can be appropriate for short-segment tumors. Through FSRT, excellent TC rates have been achieved but ARE rates (eg, obstructive hydrocephalus and pituitary dysfunction) are alarming.[85] Recent studies assessing the role of FSRT (normo- or hypo-fractionated) in the management

TABLE 3. Strategies and Recommendations for Common Issues and Concerns Regarding Radiation-Based Management of Intracranial meningiomas[a]

Consideration	Common Issues/Concerns	Possible Strategies	Typical Single Session SRS Dose Ranges
Location			
Adjacent to brainstem	Motor deficits	1. Reduced dose SRS	12-14 Gy, depending on size[83]
	Auditory dysfunction[83]	Reduce 12 Gy volume[83]	
		CI ≤2.0, HI ≤2.0, and GI ≥3.0[83]	
		2. hFSRT[86,87]	
		2.5-5 Gy × 5 fractions	
		3. PBRT	
ONSM	Radiation-induced optic neuropathy/retinopathy, pituitary dysfunction[88,89]	1. Multisession SRS (eg CK)[90]	12-14 Gy (depending on status of vision) ≤12 Gy, ensure[83] minimal 10 Gy volume of optic apparatus
		2. nFSRT/hFSRT[86,87]	
Non-ONSM but in vicinity of optic apparatus		1. Reduced dose SRS	
		Reduce 10 Gy volume[83]	
		Minimize number of isocenters[83]	
		2. nFSRT/hFSRT[86,87]	
Within cavernous sinus	Accurately contouring target volume	High-resolution, contrast-enhanced MRI	12-14 Gy
High grade			
Immediate postoperative	Greater coverage of margin required to account for remnant tumor cells	1. Increase SRS dose[58,84]	16-20 Gy[84]
		2. nFSRT/hFSRT[86,87]	14-20 Gy[84]
		3. Moderate SRS dose but wider margin[83]	
Recurrence	Radioresistance[29-32]	Increase SRS dose[58,84]	≥20 Gy[58]
Edema			
Prior to SRS, symptomatic	Greater likelihood to have post-SRS symptoms[10]	1. Surgical intervention if symptoms concerning	12-14 Gy, depending on size
		2. Reduce SRS dose + concomitant steroids	
Size			
>3-4 cm^3	Greater dose delivery to healthy tissue, increasing risk of edema and other AREs[32,59-61]	1. Microsurgical resection if patient symptomatic and lesion accessible	11-13 Gy
		2. Reduce SRS dose	
		3. nFSRT/hFSRT	

[a]CI, conformity index; CK, cyberknife; AREs, adverse radiation events; GI, gradient index; Gy, Gray; SRS, stereotactic radiosurgery; hFSRT, hypofractionated stereotactic radiotherapy; HI, heterogeneity index; nFSRT, normofractionated stereotactic radiotherapy; ONSM, optic nerve sheath meningioma.

of large, irregularly shaped skull base meningiomas have suggested favorable TC rates as well.[86,87] In both of these short-term studies, although the toxicity rate was concerning as well, it was found to be lower in the hypofractionated group (5 fractions). The possibility of creating highly conformal plans and a steep dose gradient have made proton-based irradiation an option for irregular/large basal meningiomas. Robust outcome data are limited, however. Although some small studies have demonstrated reasonable TC rates, AREs such as hearing loss, temporal lobe epilepsy, and optic neuropathy are concerning.[88,89] Such data have led to the assessment of multisession, frameless, photon-based SRS methods. In a sample of 3 patients with optic nerve sheath meningioma, an excellent TC rate and improvement of vision has been reported.[90] We await future longer-term data on larger samples of patients.

Molecular/Genetic Markers

Molecular markers can potentially improve the stratification of the natural history of meningiomas.[27,91] Two recent genome-sequencing

studies have identified novel mutations in certain types of meningiomas[92,93]; pharmaceutical agents targeting the pathways associated with some of these mutations are available and trials are under way. The complementary use of gene-targeted therapeutics, in combination with SRS and/or microsurgery, has the potential to improve outcomes and, thus, should be explored further.

Molecular markers associated with AREs require special attention. Kan et al[94] has shown VEGF and HIF-1 as predictors of post-SRS edema. A targeted approach, using bevacizumab, has the potential to improve outcomes and decrease systemic side effects, compared with corticosteroids. Several studies have assessed the efficacy of bevacizumab for this matter and even for the prevention of tumor recurrence with relatively favorable outcomes.[95-97] Early studies attempting to identify "radioprotective" agents showed moderate success in animal models, and these attempts perhaps need to be revisited.[98] Future randomized controlled trials, comparing bevacizumab and corticosteroids, are necessary to optimize methods of preventing and/or ameliorating post-SRS edema. Furthermore, prospective studies designed to identify correlations between other serological markers and radiological/clinical evidence of AREs are necessary to potentially establish additional therapeutic targets.

SRS and Adjunctive Therapy for NF2 Patients

The utility of SRS for meningiomas in NF2 patients has been established. Nunes et al,[96] assessing the utility of adjunctive therapies in the management of NF2 patients, demonstrated that bevacizumab resulted in a short-term reduction of the volume of some meningiomas; this was not permanent. Therefore, an upfront treatment with bevacizumab to induce tumor shrinkage followed by the standard SRS session may improve TC and ARE rates. Future studies are necessary to evaluate this approach.

CONCLUSION

Our evolving understanding of meningiomas will affect the future role of SRS in their management. Various pharmaceutical therapeutic approaches to optimize the effects of SRS/minimize AREs are emerging as well, and it is necessary to assess their efficacy through well-designed, randomized controlled trials. Furthermore, it is essential to continually collect and report institutional studies, including patient quality-of-life studies, to ensure optimal care.[77]

Disclosure

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

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