Cheng-Chia Lee, MD, PhD[*§§§]
Daniel M. Trifiletti, MD[‡]
Arjun Sahgal, MD[§]
Antonio DeSalles, MD[¶]
Laura Fariselli, MD[‖]
Motohiro Hayashi, MD[#]
Marc Levivier, MD[**]
Lijun Ma, PhD[‡‡]
Roberto Martínez Álvarez, MD[§§]
Ian Paddick, PhD[¶¶]
Jean Regis, MD[‖‖]
Samuel Ryu, MD[##]
Ben Slotman, MD, PhD[***]
Jason Sheehan, MD, PhD[‡‡‡]

[*]Department of Neurosurgery, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan, Republic of China; [‡]Department of Radiation Oncology, University of Virginia, Charlottesville, Virginia; [§]Department of Radiation Oncology, University of Toronto, Sunnybrook Odette Cancer Centre, Toronto, Ontario, Canada; [¶]Department of Neurosurgery, University of California Los Angeles, Los Angeles, California; [‖]Radiotherapy unit, Radiosurgery dep Istituto neurologico Carlo Besta Foundation, Milan, Italy; [#]Department of Neurosurgery, Tokyo Women's Medical University, Toyko, Japan; [**]Neurosurgery Service and Gamma Knife Center, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [‡‡]Division Physics, Department of Radiation Oncology, University of California San Francisco, San Francisco, California; [§§]Department of Radiosurgery and Functional Neurosurgery, Ruber International Hospital, Madrid, Spain; [¶¶]Division Physics, National Hospital for Neurology and Neurosurgery, London, UK; [‖‖]Department of Functional Neurosurgery, Timone University Hospital, Aix-Marseille University, Marseille, France; [##]Department of Radiation Oncology, Stony Brook University, Stony Brook, New York; [***]Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands; [‡‡‡]Department of Neurological Surgery, University of Virginia, Charlottesville, VA, USA; [§§§]School of Medicine, National Yang-Ming University, Taipei, Taiwan

Correspondence:
Cheng-chia Lee, MD,
Department of Neurosurgery,
Neurological Institute,
Taipei Veterans General Hospital,
17F, No. 201, Shih-Pai Road,
Sec. 2, Beitou, Taipei 11217,
Taiwan, Republic of China.
E-mail: cclee12@vghtpe.gov.tw

Received, August 21, 2017.
Accepted, January 5, 2018.

Stereotactic Radiosurgery for Benign (World Health Organization Grade I) Cavernous Sinus Meningiomas—International Stereotactic Radiosurgery Society (ISRS) Practice Guideline: A Systematic Review

BACKGROUND: Stereotactic radiosurgery (SRS) has become popular as a standard treatment for cavernous sinus (CS) meningiomas.

OBJECTIVE: To summarize the published literature specific to the treatment of CS meningioma with SRS found through a systematic review, and to create recommendations on behalf of the International Stereotactic Radiosurgery Society.

METHODS: Articles published from January 1963 to December 2014 were systemically reviewed. Three electronic databases, PubMed, EMBASE, and The Cochrane Central Register of Controlled Trials, were searched. Publications in English with at least 10 patients (each arm) were included.

RESULTS: Of 569 screened abstracts, a total of 49 full-text articles were included in the analysis. All studies were retrospective. Most of the reports had favorable outcomes with 5-yr progression-free survival (PFS) rates ranging from 86% to 99%, and 10-yr PFS rates ranging from 69% to 97%. The post-SRS neurological preservation rate ranged from 80% to 100%. Resection can be considered for the treatment of larger (>3 cm in diameter) and symptomatic CS meningioma in patients both receptive to and medically eligible for open surgery. Adjuvant or salvage SRS for residual or recurrent tumor can be utilized depending on factors such as tumor volume and proximity to adjacent critical organs at risk.

CONCLUSION: The literature is limited to level III evidence with respect to outcomes of SRS in patients with CS meningioma. Based on the observed results, SRS offers a favorable benefit to risk profile for patients with CS meningioma.

KEY WORDS: Cavernous sinus, Meningioma, Stereotactic radiosurgery, Systematic review, Practice guidelines

Neurosurgery 0:1–14, 2018 DOI:10.1093/neuros/nyy009 www.neurosurgery-online.com

Although most meningiomas are benign lesions, classified as World Health Organization (WHO) grade I tumors, their recurrence rates differ based on anatomic location. Meningiomas that invade the medial sphenoid wing, clinoidal region, and cavernous sinus (CS) have a relatively higher recurrence rate.[1] The natural history of CS meningiomas is, however, not fully defined, but early and late tumor progression along with accompanying morbidity is not infrequent.[1] To decrease the recurrence rate, aggressive and radical surgical removal has become a principle of CS meningioma surgery.[2,3] However, surgery for tumors in this location is associated with a relatively high incidence of cranial nerve morbidity.

In 1993, Duma reported the first series of patients with CS meningioma treated with stereotactic radiosurgery (SRS).[4] In the following years, several SRS studies on CS meningioma were reported.[5-10] Although debate continues

ABBREVIATIONS: CS, cavernous sinus; **GK,** Gamma Knife; **ICA,** internal carotid artery; **IMRT,** intensity-modulated radiation therapy; **ISRS,** International Stereotactic Radiosurgery Society; **LINAC,** linear accelerator; **MRI,** magnetic resonance imaging; **PFS,** progression-free survival; **SRS,** stereotactic radiosurgery; **SRT,** stereotactic radiotherapy; **WHO,** World Health Organization

on the optimal management of meningioma involving the CS, SRS has gradually become accepted as a standard treatment for CS meningiomas typically less than 3 cm diameter. More recently, the combination of microsurgery and SRS has been adopted in several centers as a means to reduce the morbidity of surgery while achieving the goals of decompression and tumor debulking for large meningiomas in critical locations, including the CS.[5,10,11] Fractionated stereotactic radiation, delivered over 25 to 30 treatments, has also been a long standing therapy for patients with CS meningioma, especially those that are large, adjacent to critical structures and nonoperable. The focus of this review is on single-fraction SRS; however, discussion of stereotactic radiotherapy (SRT) will be provided as comparative analyses based on the reported literature.

Under the auspices of the International Stereotactic Radiosurgery Society (ISRS) Guideline Committee, we reviewed and summarized current literature specific to SRS for CS meningioma. This aim of this review was to determine the treatment efficacy of SRS specific to CS meningioma, and the identification of risk factors in relation to treatment response.

METHODS

Article Selection

The clinical practice guideline taskforce members of the ISRS conducted a systematic review of the literature relevant to the management of CS meningioma. During the development process, the panel participated in a series of committee conferences. The panel, through an iterative process, conducted a written review.

Articles were included when they met inclusion criteria. PRISMA guidelines were followed for the analysis (PRISMA 2009). Articles that do not meet the following criteria are, for the purposes of this evidence-based clinical practice guideline, not considered appropriate evidence for this systematic review.

PubMed, EMBASE, and Cochrane Library Search Terms included ("meningioma"[Majr]) OR ("cavernous sinus"[Majr]), (meningioma* [Title/Abstract]) AND (cavernous sinus OR sella* OR parasella* OR skull base* [Title/Abstract]), (1 or 2) and (radiosurgery[Mesh] OR radiotherapy[Mesh] OR Gamma Knife OR LINAC OR Cyberknife OR proton) AND ((cavern* OR sella*) OR sinus*), and Limit to English and Humans.

To be included in this research, a study had to be an investigation that investigated human patients suspected of having a mass in the CS, allowance for mixed indications with the caveat that they reported results specific to the CS cohort or a cohort such that ≥50% of the sample were CS meningioma, enrolled a minimum of 10 patients, contained patients ≥18 yr of age. Exclusion criteria included review of meeting abstracts, historical articles, editorials, letters, commentaries, systematic reviews, or meta-analyses. If a prospective case series, reporting of baseline values, had to be stipulated, no case series with nonconsecutive enrollment of patients were permitted.

Literature Review

The articles published from January 1966 to December 2014 had been searched from 3 major databases: EMBASE, PubMed, and The Cochrane Central Register of Controlled Trials. The policy for searching these electronic databases was constructed by the evidence-based clinical practice guideline taskforce members, and the authors used previously published search strategies to identify relevant studies. Figure 1 demonstrated the process of the selection via criteria set listed above.

Of 569 screened publications, the search resulted in 120 articles, 71 were excluded based on the inclusion and exclusion criteria mentioned above. The remaining 49 articles included Gamma Knife (GK; Elekta AB, Stockholm, Sweden) SRS series (n = 32), linear accelerator (LINAC) SRS series (n = 6), a proton series (n = 1), SRT series (n = 8), and comparison between GK SRS and SRT (n = 2).

Ranking the Evidence Quality

The evidence quality was ranked by applying an evidence hierarchy developed by the ISRS Guidelines Committee for various study types; diagnostic, prognostic, therapeutic, and decision modeling. The methodology used to conduct quality evaluations of the evidence can be located by using the following link: https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology. The classification of published reports was performed according to the scheme listed in Table 1.

Strength of Recommendation Rating Scheme

Level I: high degree of clinical certainty (class I evidence or overwhelming class II evidence).

Level II: clinical certainty (class II evidence or a strong consensus of class III evidence).

Level III: clinical uncertainty (inconclusive or conflicting evidence or opinion).

RESULTS

The Effect of SRS on a Meningioma Involving the CS

SRS is usually delivered in a single fraction, but it may be delivered in up to 5 fractions in recent SRS models.[12] In this review, all series consisted of single-fraction SRS. Except for cobalt-based SRS devices such as the GK (Elekta AB), there exist on the market a number of LINAC-capable SRS modalities, for example, Varian's Edge (Palo Alto, California), Elekta's Versa HD (Elekta AB), Tomotherapy© Hi-Art© (Accuray® Inc, Sunnyvale, California), the Cyberknife (Accuray® Inc), and Novalis (BrainLab, München, Germany). In addition, charged particle SRS (eg, proton beam radiosurgery) is emerging in the literature as a viable SRS technology.[13]

Since Duma's first publication on SRS for CS meningiomas,[8] several series emerged and most of them report favorable outcomes with 5-yr progression-free survival (PFS) rates ranging from 86% to 99%, and 10-yr PFS rate ranging from 69% to 97%.[7,14-16] Although studies with long-term follow-up are relatively scant, 2 reports have reported 15- and 20-yr PFS rates ranging from 87% to 92%.[17,18] In a multi-institutional series of 4565 patients with intracranial meningiomas treated with SRS (1272 with CS meningiomas), Santacroce et al[14] demonstrated 5- and 10-yr PFS rates of 95.2% and 88.6%, respectively,

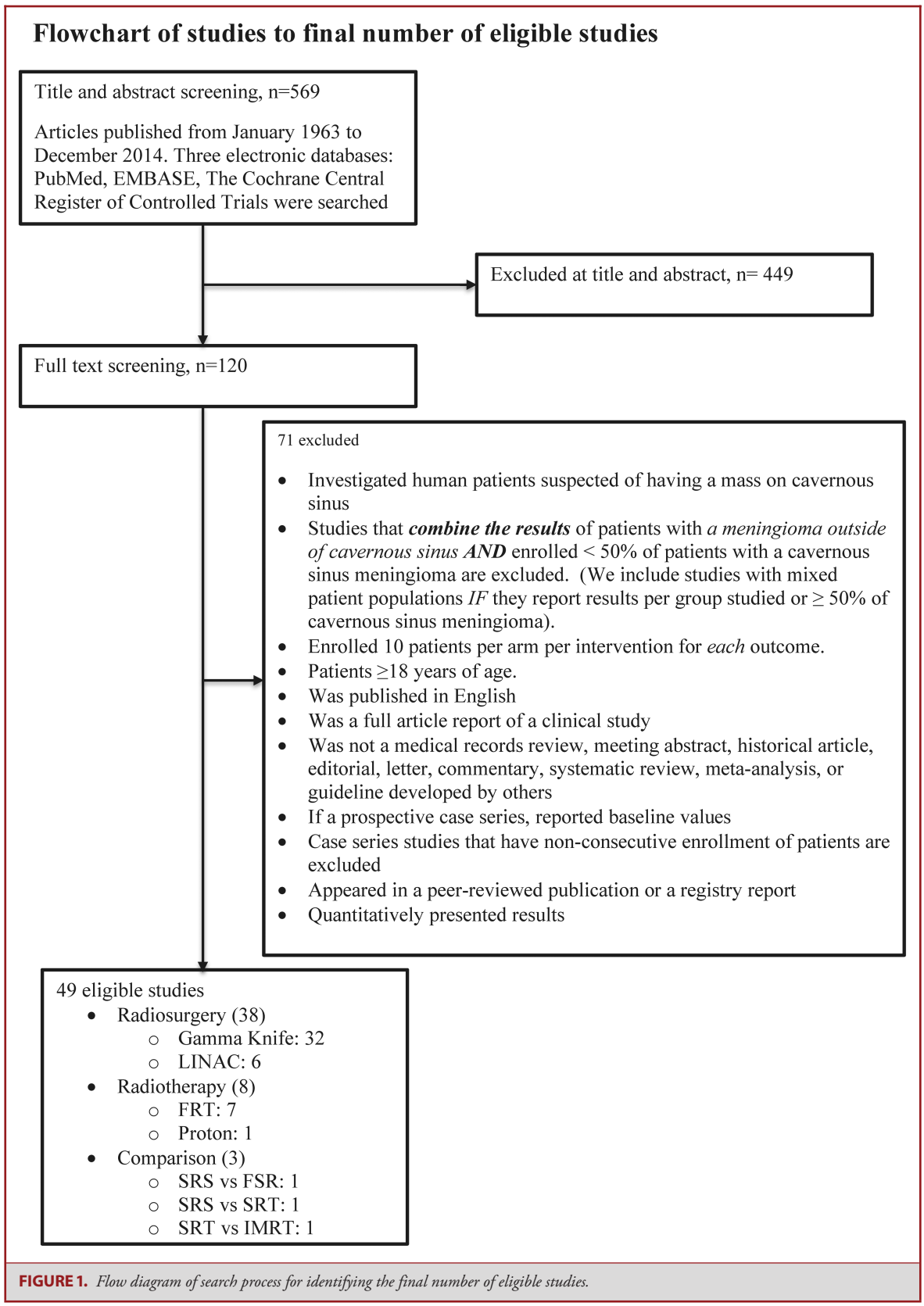

FIGURE 1. *Flow diagram of search process for identifying the final number of eligible studies.*

TABLE 1. Level of Evidence

Level I evidence	Evidence from 1 or more well-designed, randomized controlled clinical trials, including overviews of such trials.
Level II evidence	Evidence from 1 or more well-designed comparative clinical studies, such as nonrandomized cohort studies, case-control studies, and other comparable studies, including less well-designed randomized controlled trials.
Level III evidence	Evidence from case series, comparative studies with historical controls, case reports, and expert opinion, as well as significantly flawed randomized controlled trials.

and improved tumor control for skull base tumors compared to convexity tumors.

Two large single-institutional series have also been reported demonstrating favorable outcomes. The first is from Pollock et al,[15] which evaluated 115 patients with CS meningiomas demonstrating a 5- and 10-yr local tumor control rate of 99% and 93%, respectively. The second series is from the University of Pittsburgh, which published on 272 patients treated with SRS, demonstrated a 5- and 10-yr PFS rate of 94% and 86%.[16] Interestingly, their data also demonstrated that patients who underwent prior microsurgical procedures were less likely to demonstrate improvement in pre-existing cranial neuropathies, compared to those treated with SRS alone.[16]

Statistically significant ($P < .05$) factors associated with improved SRS local control outcomes were identified and included higher marginal dose, small- to medium-sized tumors, WHO grade I, upfront SRS (irradiated tumor without surgical resection), early SRS (cranial deficits < 1 yr), female sex, younger age, and less conformal plans (Table 2). The incidence of neurological deterioration, or development of new neurological deficits in those series with long-term follow-up, has been relatively low. Approximately 80% to 100% of patients preserve neurological functions (Table 2).

The median marginal dose of single-fraction SRS ranged from 11 to 19 Gy (Table 2). Data are conflicting with earlier series supporting a single fraction dose of >14 Gy as a significant predictor of local control[9,19] (level III evidence), while more modern data support lower marginal doses ranging from 11 to 12 Gy[6,20-22] (level III evidence). If we consider all types of meningioma in aggregate, a series from Mayo Clinic[23] showing that 16 Gy delivered to the tumor margin provides long-term local control (25 yr follow-up). Another series from Kuhn et al[24] suggests that 12 Gy was the minimum sufficient margin dose for the treatment of meningiomas. Below 12 Gy is as low as one should consider using for meningiomas as there is probably worsening of local control below this dose. However, these constitute level III evidence.

Primary or Adjuvant SRS

Advancements in neuroimaging improved the diagnosis of CS meningioma. As a result, there are increasing reports of SRS for CS meningioma based on a magnetic resonance imaging (MRI)-based diagnosis. Kano et al[16] evaluated the cranial nerve outcomes in patients who underwent SRS for CS meningiomas with or without prior microsurgery. They observed improvement rates specific to cranial nerve deficits after SRS of 20% at 1 yr, 34% at 2 yr, 36% at 3 yr, and 39% at 5 yr. Patients who had not undergone prior microsurgery had significantly higher improvement rates of pre-existing cranial nerve symptoms and signs ($P = .001$), suggesting that microdissection increases the risk of persistent cranial nerve dysfunction.[16]

The indications for SRS with or without prior resection vary appreciably from center to center. However, considering the generally benign nature of a CS meningioma and the high tumor control rate after SRS alone, clinician treatment preference leads to variations in treatment practices and inherent biases in the published series detailing these treatment outcomes. In this regard, further well-designed clinical trials would be necessary to ascertain the treatment priority.

Radiation Tolerance of Optic Apparatus, Cranial Nerves, and Internal Carotid Artery Abutting CS Meningiomas

The proximity of CS meningioma to the optic apparatus, cranial nerves, and internal carotid artery (ICA) needs specific consideration when using solitary high doses of radiation to CS tumors.[25] Although CS tumors frequently abut the optic nerve and/or chiasm, Tishler et al[26] reported that, with a dose to the optic nerve and chiasm of 8 Gy or less, none of their 35 patients developed a radiation-related optic neuropathy. Similarly, CS tumors typically encase adjacent cranial nerves. More recent studies reported that marginal radiation doses of 10 to 14 Gy (maximum doses of 20-28) were well tolerated and had a low risk of radiation-related optic neuropathy.[27-32] When prescribing a dose to a CS meningioma, one should be mindful of the optic apparatus and keep the radiation exposure less than 10 Gy.[33] The other cranial nerves of the CS seem to have greater tolerance for irradiation, and the treatment volume could include the majority of the CS.[33] For tolerance of other cranial nerves within the CS, there is no clear evidence showing the maximal radiation tolerance. The risk of permanent radiation-induced cranial nerve injury is rare, and the incidence is less than 1% in the most series that we collected (Tables 2 and 3). Tishler et al[26] found that a dose up to 40 Gy seems to be tolerated when treating lesions involving the II and IV cranial nerves. The new onset motor cranial nerve deficits in most series accompany tumor progression and thus are not generally occurring as a radiation-induced deficit. In the absence of tumor growth, sensory or motor cranial nerve palsies in

TABLE 2. Radiosurgery for CS Meningioma

Author, year	Study design and evidence level	Modality/ case no.	Primary/ adjuvant	Margin dose (Gy)	Tumor volume (mL)	FU (m)	Tumor control rate (%)	Progressive-free survival (%)	Neurological preservation (%)	Favorable factors	Unfavorable factors
Kondziolka[17],[a] 2014	Retrospective, Evidence class III	GKS: 290, 86 in CS	P: 154 A: 136	15	5.5	75	91%	88% and 87% (10 and 20 yr)	80% (n = 188/234) 3.1% ARE	Primary and adjuvant treatment: no difference (93% vs 89%)	Prior radiation therapy ($P < .0001$), higher grade tumor ($P < .0001$)
Gallego[45], 2014	Retrospective, Evidence class III	LINAC: 82	P: 47 A: 35	14	17.96	100	89%	95% and 84% (5 and 10 yr)	83% (n = 68/82), 4 transient	Nil	Nil
Correa[18], 2014	Retrospective, Evidence class III	SRS: 36 SRT: 38	N/A	SRS:14 SRT:50.4-54	SRS:6 SRT:23.6	73	–	99%, 92%, 92% (5, 10, 15 yr)	100% (9 patient had transient deficits)	SRS and SRT were equally safe and effective	N/A
Kano[16], 2013/2012	Retrospective, Evidence class III	GKS: 272	P:173 A:99	13	7.9	62	–	96%, 94%, 86% (at 3, 5, 10 yr)	89% (n = 243/272)	Nil	Prior resection decrease CN improve (14% vs 37%)
Pollock[15,23], 2013/2012	Retrospective, Evidence class III	GKS: 115	P: 69 A: 46	16	9.3	89	95%	99% and 93% (5 and 10 yr)	88% (n = 101/115)	Nil	Larger treatment volume associated with complication ($P = .01$)
Rong[46][b], 2013	Retrospective, Evidence class III	GKS: 84	P: 26 A: 58	15.4	25.2	40	81%	–	83% (n = 70/83)	N/A	N/A
Starke[47][a], 2012	Retrospective, Evidence class III	GKS: 255, 138 in CS	P: 109 A:146	14	5.0	78	86%	99%, 96%, 79% (3, 5, 10 yr)	90% (n = 230/255)	N/A	Age > 65 y/o ($P = 0.001$) and decreasing dose to tumor margin ($P = .05$)
Santacroce[14][a], 2012	Retrospective, Evidence class III	GKS: 4565, 1272 in CS	N/A	14	4.8	63	93%	95%, 91%, 89% (5, 7.5, 10 yr)	93%	No prior resection, grade I tumor, female, sporadic, skull base tumors (all $P < 0.001$)	Nil
Hayashi[2][b], 2012	Retrospective, Evidence class III	GKS: 120, meningioma in 19	N/A	12	N/A	55	100%	–	95% (transient VI nerve palsy)	N/A	N/A
Santos[48], 2011	Retrospective, Evidence class III	LINAC: 88	P: 47 A: 41	14	P: 3.7 A: 5.9	86.8	90%	93% and 83% (5 and 10 yr)	81% (n = 71/88), 6 transient	Nil	Nil

TABLE 2 – *continued*

Author, year	Study design and evidence level	Modality/ case no.	Primary/ adjuvant	Margin dose (Gy)	Tumor volume (mL)	FU (m)	Tumor control rate (%)	Progressive-free survival (%)	Neurological preservation (%)	Favorable factors	Unfavorable factors
Williams[10], 2011	Retrospective, Evidence class III	GKS: 138	P: 54 A: 84	13.7	7.5	84	86%	95% and 69% (5 and 10 yr)	90% (n = 124/138)	Younger age had better tumor control ($P = 0.022$)	New CN palsy is related to tumor increase ($P < .001$)
Skeie[19], 2010	Retrospective, Evidence class III	GKS: 100	P:40 A:60	12.4	7.4	82	84%	99%, 94%, 92% (1, 5, 10 yr)	94%	Higher margin dose	Atypical tumor
Spiegelmann[49], 2010/2002	Retrospective, Evidence class III	LINAC: 102	P: 69 A:33	13.5	7	67	98%	–	95% (n = 97/102)	Early radiosurgery (<1 yr CN deficit onset)	Nil
Takanashi[50], 2009	Retrospective, Evidence class III	GKS: 38	P:19 A: 19	14.8	8.6	52	96%	–	100%	N/A	N/A
Kimball[5,1], 2009	Retrospective, Evidence class III	LINAC: 49	N/A	12.5	5.9	50	98%	100% and 98% (5 and 10 yr)	98%	N/A	N/A
Han[52], 2008	Retrospective, Evidence class III	GKS: 63, 12 in CS	P:43 A:20	12.7	6.5	77	90%	90% (5 yr)	85%	Nil	Age > 70 y/o is unfavorable for a CN improvement
Kondziolka[53a], 2008	Retrospective, Evidence class III	GKS: 972, 308 in CS	P: 536 A: 424	14	7.4	48	P: 97% A: 93% Gr II: 50% Gr III: 17%	At 10 yr P: 95% A: 91%	92%	Nil	Higher grade of tumor, larger tumor volume, and multiple meningioma
Hasegawa[5], 2007	Retrospective, Evidence class III	GKS: 115	P: 49 A: 66	13	14	62	–	94% and 92% (5 and 10 yr)	89% (n = 97/109)	Small to medium-sized tumors. No prior resection had significant post-GK improvement	Nil
Zachenhofer[54], 2006	Retrospective, Evidence class III	GKS: 36	P:11 A:25	P:19 A:13 Mixed:17	P: 16 A:24 Mixed:20	103	94%	–	96% (n = 1/36)	N/A	N/A
Metellus[37], 2005	Retrospective, Evidence class III	GKS: 36 FRT: 38	P: 23GK/18FR A: 13GK/20FR	GK: 15 FR: 53	GK: 5.2 FR: 13.5	GK: 64 FR: 89	GK: 94.4 FR: 94.7	–	GK: 100% FR: 97.4%	GKS radiosurgery provides better radiological response ($P = 0.03$). No significance between p and a treatment	N/A

TABLE 2 – *continued*

Author, year	Study design and evidence level	Modality/ case no.	Primary/ adjuvant	Margin dose (Gy)	Tumor volume (mL)	FU (m)	Tumor control rate (%)	Progressive-free survival (%)	Neurological preservation (%)	Favorable factors	Unfavorable factors
Pollock[55], 2005	Retrospective, Evidence class III	GKS: 49	P:49 A:0	15.9	10.2	58	100%[a] (2 resections for s/s)	98%, 85%, 80% (1, 3, 7 yr)	86% (n = 42/49)	Nil	Nil
Liu[56b], 2005	Retrospective, Evidence class III	GKS:175, meningioma in 88	P: 85 A:90	12.1	6.6	32.5	94%	–	–	N/A	N/A
Kreil[20a], 2005	Retrospective, Evidence class III	GKS: 200	P:101 A:99	12	6.5	95	98%	99% and 97% (5 and 10 yr)	95% (n = 191/200)	N/A	N/A
Kuo[57b], 2004	Retrospective, Evidence class III	GKS: 139, meningioma in 57	P:20 A:119	15	3.4	42	97%	–	98%	N/A	N/A
Maruyama[58], 2004	Retrospective, Evidence class III	GKS: 40	P:17 A:23	16	5.4	47	–	94% (5 yr)	75% (n = 30/40)	primary CS meningiomas	tumors compressing the brainstem or smaller than 10 cm^3
Dibiase[59a], 2004	Retrospective, Evidence class III	GKS: 137, CS in 29	P: 85 A: 52	14	4.5	54	91.7%	86.2 at 5 yr	N/A	Less conformal plans to cover the dural tail	male patients, patients with a CI < 1.4, and tumor size greater than 10 cc
Iwai[6], 2003/2001	Retrospective, Evidence class III	GKS: 43	P:21 A:22	11	14.7	50	91%	92% (5 yr)	91% (n = 39/43)	N/A	N/A
Flickinger[60a], 2003	Retrospective, Evidence class III	GKS:219, CS in 75	P:219 A:0	14	5	29	97%	93% (5 and 10 yr)	91% (5 and 10 yr)	Stereotactic MR and low dose tend to have lower rate of sequelae	N/A
Lee[7], 2002	Retrospective, Evidence class III	GKS: 159	P:83 A:76	13	6.5	35	94%	A: 79% at 5 yr P: 97% at 5 yr	91% (n = 145/159)	Average tumor diameter < 3 cm or volume <15 cm3	Prior resection
Nicolato[6,1], 2002/2002	Retrospective, Evidence class III	GKS: 138	P: 68 A: 70	14.8	8.1	48	97%	96% (5 yr)	96.5% (n = 107/111)	No prior resection had better neurological recovery	N/A
Villaviscencio[62a], 2001	Retrospective, Evidence class III	LINAC:56, CS in 12	P:20 A:36	15	60.4	26	95%	–	100%	N/A	N/A

TABLE 2 – *continued*

Author, year	Study design and evidence level	Modality/ case no.	Primary/ adjuvant	Margin dose (Gy)	Tumor volume (mL)	FU (m)	Tumor control rate (%)	Progressive-free survival (%)	Neurological preservation (%)	Favorable factors	Unfavorable factors
Shin[9], 2001	Retrospective, Evidence class III	GKS: 40	P:12, A: 28	18	4.3	42	Margin dose >14 Gy, 0% recur, Margin dose 10-12 Gy: 20% recur. No SRS:100% recur	86% and 82% (3 and 10 yr)	80% (n = 32/40; mild transient in 7 pts)	margin dose >14 Gy	Histological maliganancy and partial treatment, suprasellar extension, extension in >3 direction outside CS,
Chen[63b], 2001	Retrospective, Evidence class III	GKS: 69, meningioma in 35	P: 22 A: 47	15	4.7	30	–	–	100%	Radiation expose is related to distance between CN2 and tumor, not TV	N/A
Roche[8,64], 2000	Retrospective, Evidence class III	GKS: 80	P:50 A:30	14	5.8	31	95%	93% (5 yr)	94% (n = 75/80)	N/A	N/A
Marita[64a], 1999	Retrospective, Evidence class III	GKS: 88, CS in 32	P: 39 A:49	16	10	35	98%	95% (5 yr)	88% (n = 78/88)	N/A	N/A
Liscak[22], 1999	Retrospective, Evidence class III	GKS: 67	P:43 A:24	12	7.8	19	100%	–	96%	N/A	N/A
Pendl[65], 1998	Retrospective, Evidence class III	GKS: 43	P:17 A: 24	13.2	15.4	39	100%	–	100%	N/A	N/A
Chang[66], 1998	Retrospective, Evidence class III	LINAC: 24	–	17.7	6.8	45.6	100%	100% (2 yr)	92% (n = 22/24), the other 4 transient CN deficits	N/A	N/A
Kurita[67], 1997	Retrospective, Evidence class III	GKS: 18	P:3 A: 15	17	Diameter: 23mm	35	–	86% (5 yr)	94% (n = 17/18)	N/A	N/A
Duma[4], 1993	Retrospective, Evidence class III	GKS: 34	P: 6 A: 28	10-20	Diameter <35mm	26	100%	–	94% (n = 2/34, other 2 transient)	N/A	N/A

A: adjuvant, CI: conformity index, CN: cranial nerve, CS: cavernous sinus, FRT: fractionated radiotherapy, GKS: Gamma Knife radiosurgery, Gy: gray, LINAC: Linear particle accelerator, N/A: not available, P: primary, pt: patient, SRS: stereotactic radiosurgery, MR: magnetic resonance; SRT: stereotactic radiotherapy, yr: year

[a]Whole meningioma group result, not only for CS meningioma.

[b]Whole CS tumor group result, not only for CS meningioma.

TABLE 3. Fractionated Radiotherapy for CS Meningioma

Author, year	Study design and evidence level	Modality/ case no.	Primary vs adjuvant	Dose (Gy)	Tumor volume	FU (months)	Tumor control rate (%)	Progressive-free survival (%)	Cranial nerve preservation (%)	Favorable factors	Unfavorable factors
Correa, 2014[18]	Retrospective, Evidence class III	SRS: 36 SRT: 38	N/A	SRS:14 SRT:50.4-54	SRS:6 SRT:23.6	73	–	99%, 92%, 92% (5, 10, 15 yr)	100% (9 patient had transient deficits)	SRS and SRT were equally safe and effective	N/A
Combs, 2013[36]	Retrospective, Evidence class III	FSRT: 376 IMRT: 131	P:238 A: 269	57.6	53.4	107	–	98%, 95%, 94%, 88% (1yr, 3yr, 5yr, 10 yr)	N/A	benign histology, female	N/A
Slater, 2012[13]	Retrospective, Evidence class III	Proton: 72	P: 51 A: 21	For P:57 For A:59	27.6	74		90% at 5th year	92% (68/74), 3 optic, 2 temporary ARE, 1 transient diplopia. 3 panhypopitu-itarism	N/A	Atypical histology cause poor tumor control, higher optic radiation dose cause optic neuropathy
Metellus, 2010[68]	Retrospective, Evidence class III	FCR:53	P: 28 A: 25	52.9 Gy in 29.4 fractions	12.6	83	96%	98% and 96% (5 and 10 yr)	98% (permanent), 94% (transient)	N/A	N/A
Litre[69], 2009	Retrospective, Evidence class III	FSR: 100	P: 74 A:26	45Gy	N/A	33	97%	94% (3 and 7 yr)	97%	N/A	N/A
Milker-Zabel[70], 2006/2005	Retrospective, Evidence class III	FSRT:57	P: 29 A: 28	57.6	35.2	78	100%	–	100%	N/A	N/A
Brell.[71] 2006/2003	Retrospective, Evidence class III	FSRT:30	P: 29 A: 28	52	11.3	50	96%	93% (4 yr)	96%	none	none
Metellus[37], 2005	Retrospective, Evidence class III	GKS: 36 FR: 38	P: 23GK/18FR A: 13GK/20FR	GK: 15 FR: 53	GK: 5.2 FR: 13.5	GK: 64 FR: 89	GK: 94.4 FR: 94.7	–	GK: 100% FR: 97.4%	GKS radiosurgery provides better radiological response ($P = 0.03$). No significance between p and a treatment	N/A
Selch[72], 2004	Retrospective, Evidence class III	SRT: 45	P:16 A:29	50.4	14.5	36	98%	97% (3 yr)	98%	N/A	N/A
Dufour[73], 2001	Retrospective, Evidence class III	RT: 31	P:14 A:17	52	–	73	–	93% (10 yr)	100%	Tumor control rates are equal with/without surgical resection	N/A
Maguire[74], 1999	Retrospective, Evidence class III	RT: 28	P:22 A:6	53.1	–	41	–	81% (8 yr)	Orbital sac fibrosis, and decline of cognitive function	None	None

A: adjuvant, CI: conformity index, CN: cranial nerve, CS: cavernous sinus, FCR: fractionated conformal radiotherapy, FRT: fractionated radiotherapy, FSRT: fractionated stereotactic radiotherapy, GKS: Gamma Knife radiosurgery, Gy: gray, IMRT: intensity-modulated radiation therapy, LINAC: Linear particle accelerator, N/A: not available, P: primary, pt: patient, RT: radiotherapy, SRS: stereotactic radiosurgery, SRT: stereotactic radiotherapy, yr: year

SRS-treated CS meningiomas occur very infrequently when using contemporary dose and delivery techniques.[14,17]

For the ICA, the maximum tolerated dose of radiation is controversial. Some rare case reports have described ICA stenosis after SRS for parasellar, suprasellar, and CS lesions.[34,35] However, this clinical question lacks a large and long-term series for analysis. In current radiosurgery practice, the high-dose radiation volume usually includes the ICA; the risk of long-term changes in the vessel wall of the ICA appears, anecdotally, to be a very rare phenomenon.

Comparing SRS, Proton SRS/Radiotherapy, Fractionated SRT, and Conventional Radiotherapy

There are no level I or II comparisons of SRS, proton SRS or radiotherapy, SRT, or other sophisticated radiotherapy techniques (eg, intensity-modulated radiation therapy [IMRT]) for CS meningioma (Table 3).

Non–case-matched studies[18,36,37] from 3 level III studies with tumor control rates for SRS, or SRT, or IMRT demonstrated that they were similarly safe and efficient techniques in treatment of a CS meningioma although various methods, various doses, various schemes of radiation, various indications, volumes, and prior management. Metellus' report[37] showed neurological improvement for 63% patients who underwent SRT, and for 54% patients who underwent SRS ($P > .05$). Combs et al,[36] in 2013, compared the efficacy and safety between both the groups (105 CS meningiomas) who underwent either SRT or IMRT with a median total dose of 57.6 Gy, and they found no significant differences. Correa et al,[18] in 2014, also published similar results in both groups who underwent either SRS or SRT. However, radiologically 29% of patients who underwent SRT, and 53% of patients who underwent SRS, showed tumor shrinkage ($P < .04$).[37] The result implied that SRS offered a higher rate of tumor shrinkage, but no significance in clinical improvement.

Based upon these limited data, high-level evidence is needed to define the optimal radiation approach for patients with a CS meningioma. Based upon current available evidence, SRS and SRT confer favorable benefit to risk profiles for most patients with CS meningioma, eligible for either therapy.

DISCUSSION

The clinical management of a patient with a CS meningioma is challenging. The fear of causing massive bleeding and critical neurovascular structural damage has led both surgeons and patients to proceed cautiously with attempts at resection. SRS and SRT approaches have been proven in many retrospective studies to have a favorable therapeutic impact with a minimal complication rate. From this systematic review, after SRS most of the reports had favorable outcomes with 5-yr PFS rates ranging from 86% to 99%, and 10-yr PFS rate ranging from 69% to 97%. Post-SRS neurological preservation rates ranged from 80% to 100% (Table 2). Median margin dose selection is dependent on the tumor volume, anatomic relationship to the adjacent associated neurovascular structures, and physician preference. Reported SRS doses generally varied from 11 to 19 Gy; however, the optimal single-session SRS dose for a CS meningioma is a subject of debate and requires careful selection on a case by case basis. Fortunately, more and more modern data support that a lower marginal dose ranging from 12 Gy is sufficient for a benign CS meningioma.[6,20-22] Furthermore, by using a lower dose in the CS or by hypofractionating with modern SRS devices, more tumors become eligible for radiosurgery due to limits of optic apparatus to SRS.[38,39]

SRS can be delivered as either adjuvant therapy for residual tumors after subtotal resection, at the time of progression for residual disease observed, or as primary therapy for unresectable tumors. Little to no substantive differences in local tumor control or neurological outcome have been reported following SRS for primary therapy as compared to adjuvant SRS for WHO grade I meningioma. Many of the published clinical series aggregate results of patients treated with upfront SRS alone, SRS of a residual after resection (but before evidence of demonstrable growth on serial neuroimaging), and SRS at the time of tumor progression. In part, the ambiguity pertaining to the natural history of CS meningiomas and the treatment preferences of clinicians lead to variations in treatment practices and inherent biases in the published series detailing these treatment outcomes. Patient preference and fitness for a radiation modality will also naturally impact the decision to proceed with a primary or adjuvant radiation treatment.

With primary SRS for a CS meningioma, histopathologic evaluation for unfavorable features is unavailable (eg, or atypical/anaplastic meningioma). However, after SRS, the tumor responses may differ compared to other CS tumors, and are valuable in confirming the initial radiographic impression. Figure 2 illustrates 3 different response patterns of these CS tumors. The tumor volume of a CS meningioma after SRS is typically quite stable, and they rarely regressed within 2 yr. If an unpredictable tumor response is noted, we recommend to re-examine the MRI, presentation of clinical course, and re-establishing the pathological diagnosis with biopsy, as necessary.

Currently, the optimum follow-up strategy is debated: a median of 95% and 90% of tumors achieved a steady state in 5 and 10 yr, respectively. It would be reasonable to observe the tumor for the initial several years after radiosurgery, and it provides sufficient evidence regarding its propensity to grow and therefore the requirement for further treatment or more radiological follow-up.[40] Routine radiological follow-up could be extended to a longer interval after the tumor has attained a steady state and clinical follow-up with routine neurological exams and ophthalmological assessment should be continued.

In this review, the role of hypofractionated SRS and SRT for a CS meningioma was also explored,[18,36,37] particularly those exhibiting larger volumes or in close proximity to critical structures. For those CS meningioma patients with a larger volume tumor, a more diffusely infiltrative one, or one with suprasellar or

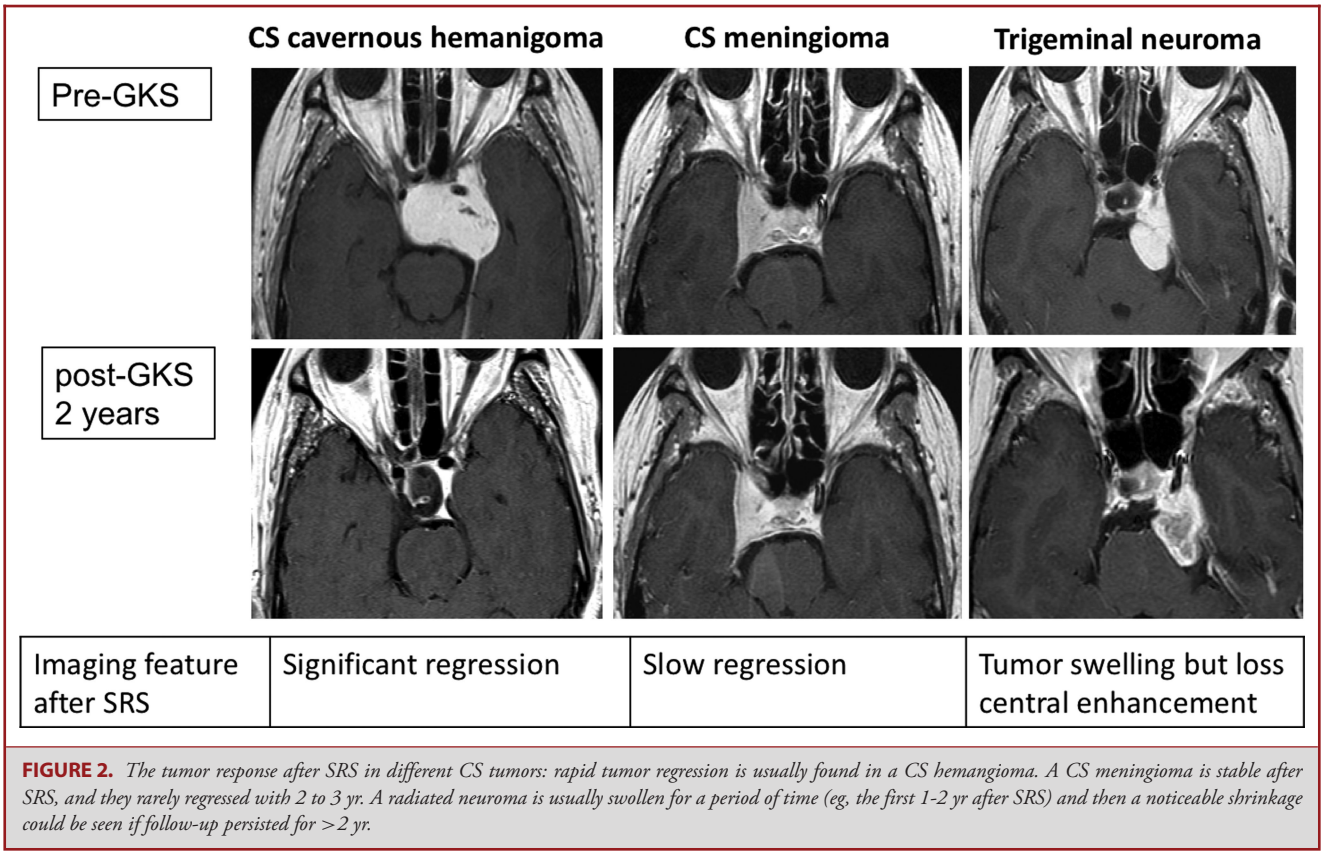

FIGURE 2. *The tumor response after SRS in different CS tumors: rapid tumor regression is usually found in a CS hemangioma. A CS meningioma is stable after SRS, and they rarely regressed with 2 to 3 yr. A radiated neuroma is usually swollen for a period of time (eg, the first 1-2 yr after SRS) and then a noticeable shrinkage could be seen if follow-up persisted for >2 yr.*

brainstem extension, SRT can be considered so as to minimize the risk of complications and optimize tumor coverage.[41] For larger meningiomas or for ones with pre-existing edema, hypofractionated SRT may have less likelihood of causing postradiosurgical edema than single-fraction SRS for meningioma.[42] Based upon the number of publications meeting eligibility criteria for this guidelines project, contemporary management with SRS represents a common approach for management of small to moderately sized CS meningiomas. In general, clinicians must select the approach (SRS, SRT, IMRT, or proton) that permits a highly targeted irradiation of the CS meningioma while still achieving a dose considered tolerable to adjacent critical structures based upon radiotoxicity guidelines such as the Quantitative Analyses of Normal Tissue Effects in the Clinic studies.[43] De Salles et al,[41] in 2002, attempted to develop a grading system to guide treatment selection, either SRS or SRT. They concluded that a meningioma well contained in the CS, with typical radiological characteristics, may be treated successfully with SRS alone with excellent outcomes. On the other hand, SRT may be favored when adjuvant treatment is necessary after subtotal resection of tumor encasing eloquent structures, where SRS is not advisable. No matter which radiation modalities clinicians choose, effort should be made to minimize irradiated volumes to prevent long-term complications, maximize the therapeutic efficacy to target tissue, and lessen the burden of the procedure(s) for the patient whenever possible.

Key Areas for Future Investigation

- The timing of SRS or SRT after prior resection warrants further investigation.
- While SRS and radiation therapy are frequently used as an upfront treatment for those with a CS meningioma, there is no level I evidence report of primary SRS as a management for a CS meningioma. Longer follow-up report for this treatment approach is warranted.
- The role of hypofractionated SRS for a CS meningioma, particularly those exhibiting larger volumes or in close proximity to critical structures, has been explored in limited publications. Optimal dose and fractionation schemes particularly for SRS of a CS meningioma should be explored.
- The neurocognitive effects of SRS and SRT in CS meningioma patients warrants further study with the use of validated neurocognitive tests and appropriate assessment intervals. There are little data on the neurocognitive functions after treating neuropathology in the CS. In 1 study of SRS for pituitary adenomas many of which resided in the CS, there was neurocognitive preservation in the patients after SRS.[44] Although it is thought that the much lower integral dose of

TABLE 4. Recommendations for Management of CS Meningioma

Evidence level	
Level III	SRS/SRT is recommended as a primary/upfront treatment option for an asymptomatic, or mildly symptomatic CS meningioma. The recurrence rate is not appreciably different between primary or adjuvant therapy for a CS meningioma
Level III	Resection should be considered for the treatment of larger and symptomatic CS meningioma in patients both receptive to, and medically eligible, for open surgery
Level III	SRS/SRT delivered to a CS meningioma has a low risk of complications; most cranial nerve functions are preserved or improved due to tumor shrinkage. Carotid artery stenosis after SRS is rare.
Level III	When no residual tumor is observed, or only a small tumor lining on the dura of the CS exists postoperatively, serial neuroimaging studies is not unreasonable. At the time of recurrence or progression of residual tumor, SRS/SRT should be considered
Level III	In patients with a CS meningioma that has rapidly and substantially recurred after prior treatment, a subtotal surgical resection or biopsy may be considered. More aggressive features of the tumor (transformation of the tumor from WHO grade I to a higher grade) should be ruled out. These tumors have a predilection for progression and postoperative SRS/SRT with a higher dose should be strongly considered.
Level III	The technique for SRS or SRT delivery will depend upon the tumor histology, tumor volume and proximity of the tumor to adjacent critical structures (eg, the optic chiasm). SRS using single session marginal doses of 11 to 16 Gy offers a local tumor control rate of 90% or higher at 5 yr post-SRS.

SRS probably mitigates neurocognitive deficits as compared to radiotherapy, more definitive studies are required to study neurocognition in a prospective fashion in SRS-treated CS meningioma patients.

- Limits of dose to the optic apparatus also need better clarification, as it defines the approach, either single or hypofractionated SRS or SRT.
- Higher quality evidence comparing SRS, SRT, IMRT, and charged particle techniques and devices is needed to help guide clinicians on the specific indications and limitations of each approach for patients with a CS meningioma.
- Comparisons of SRS-treated CS meningioma patients to a control group of untreated meningioma patients.
- Comparative studies are required of specific radiosurgery and radiation therapy devices to assess for differences in outcome. Similarly, comparative studies evaluating the effects of proficiency and volume of a center on outcome should be performed.

CONCLUSION

SRS plays an important role in the management of patients with a CS meningioma. SRS is typically performed in patients with demonstrable residual tumor or tumor recurrence after resection. However, the upfront treatment using SRS for a CS meningioma has gained popularity in recent years. For those with a radiographically diagnosed CS meningioma, the post-SRS tumor response can reconfirm the diagnosis of meningioma. Radiographic signs of progression in the setting of younger patients or patients with symptoms attributable to progression should be more strongly considered for intervention. Post-SRS cranial nerve deterioration is rare, while improvement in cranial nerve function is not uncommon. Longer and more meticulous follow-up report is warranted.

Higher levels of evidence are needed to define the optimal treatment approach for patients with CS meningiomas. Based upon available evidence, SRS and SRT confer favorable risk-benefit profiles than conventional radiotherapy for most patients with a CS meningioma. Further insights may be achieved through prospective radiosurgical registries (Table 4).

Disclosures

This evidence-based clinical practice guideline was supported by the International Stereotactic Radiosurgery Society. No funding from outside commercial sources to support the development of this work. Dr Martínez Álvarez is a consultant for Elekta AB. Dr Sahgal has grants from Elekta AB and education honoraria from previous education seminars from Elekta AB, Varian Medical Systems, Accuray, and Medtronic (kyphoplasty division). Dr Slotman has a research grant and speaker honorarium from Varian Medical Systems and speaker honorarium from ViewRay. Dr Paddick is a consultant for and has received a research grant from Elekta, AB. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Disclaimer

These guidelines should not be considered inclusive of all methods of care or exclusive of other methods or care reasonably directed to obtain similar results. The physician must make the ultimate judgment depending on characteristics and circumstances of individual patients. Adherence to this guideline will not ensure successful treatment in every situation. The authors of this guideline and the International Society of Stereotactic Radiosurgery assume no liability for the information, conclusions, and recommendations contained in this report.

REFERENCES

1. Mathiesen T, Lindquist C, Kihlstrom L, Karlsson B. Recurrence of cranial base meningiomas. *Neurosurgery*. 1996;39(1):2-7; discussion 8-9.
2. De Jesus O, Sekhar LN, Parikh HK, Wright DC, Wagner DP. Long-term follow-up of patients with meningiomas involving the cavernous sinus: recurrence, progression, and quality of life. *Neurosurgery*. 1996;39(5):915-919; discussion 919-920.
3. DeMonte F, Smith HK, al-Mefty O. Outcome of aggressive removal of cavernous sinus meningiomas. *Journal of neurosurgery*. 1994;81(2):245-251.

4. Duma CM, Lunsford LD, Kondziolka D, Harsh GRt, Flickinger JC. Stereotactic radiosurgery of cavernous sinus meningiomas as an addition or alternative to microsurgery. *Neurosurgery*. 1993;32(5):699-704; discussion 704-695.
5. Hasegawa T, Kida Y, Yoshimoto M, Koike J, Iizuka H, Ishii D. Long-term outcomes of Gamma Knife surgery for cavernous sinus meningioma. *Journal of neurosurgery*. 2007;107(4):745-751.
6. Iwai Y, Yamanaka K, Ishiguro T. Gamma knife radiosurgery for the treatment of cavernous sinus meningiomas. *Neurosurgery*. 2003;52(3):517-524; discussion 523-514.
7. Lee JY, Niranjan A, McInerney J, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery providing long-term tumor control of cavernous sinus meningiomas. *Journal of neurosurgery*. 2002;97(1):65-72.
8. Roche PH, Regis J, Dufour H, et al. Gamma knife radiosurgery in the management of cavernous sinus meningiomas. *Journal of neurosurgery*. 2000;93 Suppl 3:68-73.
9. Shin M, Kurita H, Sasaki T, et al. Analysis of treatment outcome after stereotactic radiosurgery for cavernous sinus meningiomas. *Journal of neurosurgery*. 2001;95(3):435-439.
10. Williams BJ, Yen CP, Starke RM, et al. Gamma Knife surgery for parasellar meningiomas: long-term results including complications, predictive factors, and progression-free survival. *Journal of neurosurgery*. 2011;114(6):1571-1577.
11. O'Sullivan MG, van Loveren, Tew HR, Jr JM. The surgical resectability of meningiomas of the cavernous sinus. *Neurosurgery*. 1997;40(2):238-244; discussion 245-237.
12. Barnett GH, Linskey ME, Adler JR, et al. Stereotactic radiosurgery–an organized neurosurgery-sanctioned definition. *Journal of neurosurgery*. 2007;106(1):1-5.
13. Slater JD, Loredo LN, Chung A, et al. Fractionated proton radiotherapy for benign cavernous sinus meningiomas. *International journal of radiation oncology, biology, physics*. 2012;83(5):e633-637.
14. Santacroce A, Walier M, Regis J, et al. Long-term tumor control of benign intracranial meningiomas after radiosurgery in a series of 4565 patients. *Neurosurgery*. 2012;70(1):32-39; discussion 39.
15. Pollock BE, Stafford SL, Link MJ, Garces YI, Foote RL. Single-fraction radiosurgery of benign cavernous sinus meningiomas. *Journal of neurosurgery*. 2013;119(3):675-682.
16. Kano H, Park KJ, Kondziolka D, et al. Does prior microsurgery improve or worsen the outcomes of stereotactic radiosurgery for cavernous sinus meningiomas? *Neurosurgery*. 2013;73(3):401-410.
17. Kondziolka D, Patel AD, Kano H, Flickinger JC, Lunsford LD. Long-term Outcomes After Gamma Knife Radiosurgery for Meningiomas. *American journal of clinical oncology*. 2014.
18. Correa SF, Marta GN, Teixeira MJ. Neurosymptomatic carvenous sinus meningioma: a 15-years experience with fractionated stereotactic radiotherapy and radiosurgery. *Radiation oncology*. 2014;9:27.
19. Skeie BS, Enger PO, Skeie GO, Thorsen F, Pedersen PH. Gamma knife surgery of meningiomas involving the cavernous sinus: long-term follow-up of 100 patients. *Neurosurgery*. 2010;66(4):661-668; discussion 668-669.
20. Kreil W, Luggin J, Fuchs I, Weigl V, Eustacchio S, Papaefthymiou G. Long term experience of gamma knife radiosurgery for benign skull base meningiomas. *Journal of neurology, neurosurgery, and psychiatry*. 2005;76(10):1425-1430.
21. Hayashi M, Chernov M, Tamura N, et al. Gamma knife radiosurgery for benign cavernous sinus tumors: treatment concept and outcomes in 120 cases. *Neurologia medico-chirurgica*. 2012;52(10):714-723.
22. Liscak R, Simonova G, Vymazal J, Janouskova L, Vladyka V. Gamma knife radiosurgery of meningiomas in the cavernous sinus region. *Acta neurochirurgica*. 1999;141(5):473-480.
23. Pollock BE, Stafford SL, Link MJ. Stereotactic radiosurgery of intracranial meningiomas. *Neurosurg Clin N Am*. 2013;24(4):499-507.
24. Kuhn EN, Taksler GB, Dayton O, et al. Patterns of recurrence after stereotactic radiosurgery for treatment of meningiomas. *Neurosurgical focus*. 2013;35(6):E14.
25. Bentzen SM, Constine LS, Deasy JO, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *International journal of radiation oncology, biology, physics*. 2010;76(3 Suppl):S3-9.
26. Tishler RB, Loeffler JS, Lunsford LD, et al. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. *International journal of radiation oncology, biology, physics*. 1993;27(2):215-221.
27. Jinhu Y, Jianping D, Xin L, Yuanli Z. Dynamic enhancement features of cavernous sinus cavernous hemangiomas on conventional contrast-enhanced MR imaging. *AJNR. American journal of neuroradiology.* 2008;29(3):577-581.
28. Leavitt JA, Stafford SL, Link MJ, Pollock BE. Long-term evaluation of radiation-induced optic neuropathy after single-fraction stereotactic radiosurgery. *International journal of radiation oncology, biology, physics*. 2013;87(3):524-527.
29. Leber KA, Bergloff J, Pendl G. Dose-response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. *Journal of neurosurgery*. 1998;88(1):43-50.
30. Mori K, Handa H, Gi H, Mori K. Cavernomas in the middle fossa. *Surgical neurology*. 1980;14(1):21-31.
31. Nakamura N, Shin M, Tago M, et al. Gamma knife radiosurgery for cavernous hemangiomas in the cavernous sinus. Report of three cases. *Journal of neurosurgery*. 2002;97(5 Suppl):477-480.
32. Pollock BE, Link MJ, Leavitt JA, Stafford SL. Dose-volume analysis of radiation-induced optic neuropathy after single-fraction stereotactic radiosurgery. *Neurosurgery*. 2014;75(4):456-460; discussion 460.
33. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys*. 2010;37(8):4078-4101.
34. Lombardi D, Giovanelli M, de Tribolet N. Sellar and parasellar extra-axial cavernous hemangiomas. *Acta neurochirurgica*. 1994;130(1-4):47-54.
35. Abeloos L, Levivier M, Devriendt D, Massager N. Internal carotid occlusion following gamma knife radiosurgery for cavernous sinus meningioma. *Stereotactic and functional neurosurgery*. 2007;85(6):303-306.
36. Combs SE, Adeberg S, Dittmar JO, et al. Skull base meningiomas: Long-term results and patient self-reported outcome in 507 patients treated with fractionated stereotactic radiotherapy (FSRT) or intensity modulated radiotherapy (IMRT). *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2013;106(2):186-191.
37. Metellus P, Regis J, Muracciole X, et al. Evaluation of fractionated radiotherapy and gamma knife radiosurgery in cavernous sinus meningiomas: treatment strategy. *Neurosurgery*. 2005;57(5):873-886; discussion 873-886.
38. Adler JR, Jr., Gibbs IC, Puataweepong P, Chang SD. Visual field preservation after multisession cyberknife radiosurgery for perioptic lesions. *Neurosurgery*. 2006;59(2):244-254; discussion 244-254.
39. Nguyen JH, Chen CJ, Lee CC, et al. Multisession gamma knife radiosurgery: a preliminary experience with a noninvasive, relocatable frame. *World Neurosurg*. 2014;82(6):1256-1263.
40. Cohen-Inbar O, Tata A, Moosa S, Lee CC, Sheehan JP. Stereotactic radiosurgery in the treatment of parasellar meningiomas: long-term volumetric evaluation. *Journal of neurosurgery*. 2017:1-11.
41. De Salles AA, Frighetto L, Grande CV, et al. Radiosurgery and stereotactic radiation therapy of skull base meningiomas: proposal of a grading system. *Stereotactic and functional neurosurgery*. 2001;76(3-4):218-229.
42. Unger KR, Lominska CE, Chanyasulkit J, et al. Risk factors for posttreatment edema in patients treated with stereotactic radiosurgery for meningiomas. *Neurosurgery*. 2012;70(3):639-645.
43. Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J. Radiation dose-volume effects of optic nerves and chiasm. *International journal of radiation oncology, biology, physics*. 2010;76(3 Suppl):S28-35.
44. Tooze A, Hiles CL, Sheehan JP. Neurocognitive changes in pituitary adenoma patients after gamma knife radiosurgery: a preliminary study. *World Neurosurg*. 2012;78(1-2):122-128.
45. Mari Pascual Gallego JS, Jose Carlos Bustos, Jose Angel Gutierrez Diaz, Marisa Gonzalez, Kita Sallabanda. Long-Term Follow-Up of 82 Cavernous Sinus Meningiomas Treated with Radiosurgery. *Journal of Cancer Therapy*. 2014;5:1005-1011.
46. Rong HT, Hui XH, Ju Y, Ma L, Zhang Q, Chen J. Gamma Knife Radiosurgery for Cavernous Sinus Tumors: A Report of 84 Cases. *Neurosurgery Quarterly*. 2013;23(4):239-243.
47. Starke RM, Williams BJ, Hiles C, Nguyen JH, Elsharkawy MY, Sheehan JP. Gamma knife surgery for skull base meningiomas. *Journal of neurosurgery*. 2012;116(3):588-597.
48. dos Santos MA, de Salcedo JB, Gutierrez Diaz JA, et al. Long-term outcomes of stereotactic radiosurgery for treatment of cavernous sinus meningiomas. *International journal of radiation oncology, biology, physics*. 2011;81(5):1436-1441.
49. Spiegelmann R, Nissim O, Menhel J, Alezra D, Pfeffer MR. Linear accelerator radiosurgery for meningiomas in and around the cavernous sinus. *Neurosurgery*. 2002;51(6):1373-1379; discussion 1379-1380.
50. Takanashi M, Fukuoka S, Hojyo A, Sasaki T, Nakagawara J, Nakamura H. Gamma knife radiosurgery for skull-base meningiomas. *Progress in neurological surgery*. 2009;22:96-111.

51. Kimball MM, Friedman WA, Foote KD, Bova FJ, Chi YY. Linear accelerator radiosurgery for cavernous sinus meningiomas. *Stereotactic and functional neurosurgery*. 2009;87(2):120-127.
52. Han JH, Kim DG, Chung HT, et al. Gamma knife radiosurgery for skull base meningiomas: long-term radiologic and clinical outcome. *International journal of radiation oncology, biology, physics*. 2008;72(5):1324-1332.
53. Kondziolka D, Mathieu D, Lunsford LD, et al. Radiosurgery as definitive management of intracranial meningiomas. *Neurosurgery*. 2008;62(1):53-58; discussion 58-60.
54. Zachenhofer I, Wolfsberger S, Aichholzer M, et al. Gamma-knife radiosurgery for cranial base meningiomas: experience of tumor control, clinical course, and morbidity in a follow-up of more than 8 years. *Neurosurgery*. 2006;58(1):28-36; discussion 28-36.
55. Pollock BE, Stafford SL. Results of stereotactic radiosurgery for patients with imaging defined cavernous sinus meningiomas. *International journal of radiation oncology, biology, physics*. 2005;62(5):1427-1431.
56. Liu AL, Wang C, Sun S, Wang M, Liu P. Gamma knife radiosurgery for tumors involving the cavernous sinus. *Stereotactic and functional neurosurgery*. 2005;83(1):45-51.
57. Kuo JS, Chen JC, Yu C, et al. Gamma knife radiosurgery for benign cavernous sinus tumors: quantitative analysis of treatment outcomes. *Neurosurgery*. 2004;54(6):1385-1393; discussion 1393-1384.
58. Maruyama K, Shin M, Kurita H, Kawahara N, Morita A, Kirino T. Proposed treatment strategy for cavernous sinus meningiomas: a prospective study. *Neurosurgery*. 2004;55(5):1068-1075.
59. DiBiase SJ, Kwok Y, Yovino S, et al. Factors predicting local tumor control after gamma knife stereotactic radiosurgery for benign intracranial meningiomas. *International journal of radiation oncology, biology, physics*. 2004;60(5):1515-1519.
60. Flickinger JC, Kondziolka D, Maitz AH, Lunsford LD. Gamma knife radiosurgery of imaging-diagnosed intracranial meningioma. *International journal of radiation oncology, biology, physics*. 2003;56(3):801-806.
61. Nicolato A, Foroni R, Alessandrini F, Maluta S, Bricolo A, Gerosa M. The role of Gamma Knife radiosurgery in the management of cavernous sinus meningiomas. *International journal of radiation oncology, biology, physics*. 2002;53(4):992-1000.
62. Villavicencio AT, Black PM, Shrieve DC, Fallon MP, Alexander E, Loeffler JS. Linac radiosurgery for skull base meningiomas. *Acta neurochirurgica*. 2001;143(11):1141-1152.
63. Chen JC, Giannotta SL, Yu C, Petrovich Z, Levy ML, Apuzzo ML. Radiosurgical management of benign cavernous sinus tumors: dose profiles and acute complications. *Neurosurgery*. 2001;48(5):1022-1030; discussion 1030-1022.
64. Morita A, Coffey RJ, Foote RL, Schiff D, Gorman D. Risk of injury to cranial nerves after gamma knife radiosurgery for skull base meningiomas: experience in 88 patients. *Journal of neurosurgery*. 1999;90(1):42-49.
65. Pendl G, Schrottner O, Eustacchio S, Ganz JC, Feichtinger K. Cavernous sinus meningiomas–what is the strategy: upfront or adjuvant gamma knife surgery? *Stereotactic and functional neurosurgery*. 1998;70 Suppl 1:33-40.
66. Chang SD, Adler JR, Jr., Martin DP. LINAC radiosurgery for cavernous sinus meningiomas. *Stereotactic and functional neurosurgery*. 1998;71(1):43-50.
67. Kurita H, Sasaki T, Kawamoto S, et al. Role of radiosurgery in the management of cavernous sinus meningiomas. *Acta Neurol Scand*. 1997;96(5):297-304.
68. Metellus P, Batra S, Karkar S, et al. Fractionated conformal radiotherapy in the management of cavernous sinus meningiomas: long-term functional outcome and tumor control at a single institution. *International journal of radiation oncology, biology, physics*. 2010;78(3):836-843.
69. Litre CF, Colin P, Noudel R, et al. Fractionated stereotactic radiotherapy treatment of cavernous sinus meningiomas: a study of 100 cases. *International journal of radiation oncology, biology, physics*. 2009;74(4):1012-1017.
70. Milker-Zabel S, Zabel A, Schulz-Ertner D, Schlegel W, Wannenmacher M, Debus J. Fractionated stereotactic radiotherapy in patients with benign or atypical intracranial meningioma: long-term experience and prognostic factors. *International journal of radiation oncology, biology, physics*. 2005;61(3):809-816.
71. Brell M, Villa S, Teixidor P, et al. Fractionated stereotactic radiotherapy in the treatment of exclusive cavernous sinus meningioma: functional outcome, local control, and tolerance. *Surgical neurology*. 2006;65(1):28-33; discussion 33-24.
72. Selch MT, Ahn E, Laskari A, et al. Stereotactic radiotherapy for treatment of cavernous sinus meningiomas. *International journal of radiation oncology, biology, physics*. 2004;59(1):101-111.
73. Dufour H, Muracciole X, Metellus P, Regis J, Chinot O, Grisoli F. Long-term tumor control and functional outcome in patients with cavernous sinus meningiomas treated by radiotherapy with or without previous surgery: is there an alternative to aggressive tumor removal? *Neurosurgery*. 2001;48(2):285-294; discussion 294-286.
74. Maguire PD, Clough R, Friedman AH, Halperin EC. Fractionated external-beam radiation therapy for meningiomas of the cavernous sinus. *International journal of radiation oncology, biology, physics*. 1999;44(1):75-79.

COMMENTS

The authors present a thorough review of the use of SRS for cavernous sinus meningiomas. SRS represents a standard treatment option for cavernous sinus meningiomas and when appropriately used, has significant advantages over open surgery and conventionally fractionated radiotherapy. While the benefit of surgery is the acquisition of tumor tissue and appropriate grading of the tumor, surgery in the cavernous sinus has a much higher rate of morbidity than SRS. The disadvantage of conventionally fractionated radiotherapy is the cognitive toxicity given the higher integral doses delivered to the brain and the fact that the hippocampus borders the lateral aspect of the cavernous sinus. Future questions to be explored include the indications and dose limitations for hypofractionation and the long-term efficacy of SRS when lower doses (eg 12–14 Gy to the tumor margin) are used.

Michael Chan
Winston-Salem, North Carolina

The International Stereotactic Radiosurgery Society was founded in 1995 in order to increase the dialog related to the then still emerging field of radiosurgery. Since that time multidisciplinary meetings and even a journal have emerged to further analyze the role, indications, and results of radiosurgery using a variety of platforms to perform the procedure. In general, such dialog is beneficial to current and future users and can avoid recreating the same issues or trying to resolve the same problems that have been addressed in prior years of meetings and publications.

The present report summarizes publications related to the management of cavernous sinus meningiomas using stereotactic radiosurgery. I think it is reasonable to restate what we have learned over the years for this mostly benign histology tumor that develops in a location that is not curable by microsurgical or endoscopic techniques.

1. Most are grade 1

2. Stereotactic Radiosurgery is associated with long-term tumor control (10-20 years) in >85% of patients.

3. Prior partial surgical removal often results in increased cranial nerve deficits that do not recover in most patients.

4. Tumor control can be achieved in such patients if the tumor margin dose is 12 Gy or greater.

5. Patients treated primarily (no prior surgery) have a greater chance (perhaps 40%) of improved cranial nerve function. In contrast, prior surgery reduces by half the chance of cranial nerve recovery. Motor cranial nerves have a low risk of worsening unless tumor growth occurs despite radiosurgery

6. The structure at risk is the optic nerve and efforts to keep the optic apparatus average dose <8 Gy with a maximal dose within the optic system of less than 10 provides safety.

7. Most outcomes, including those with the longest follow-up have been reported after radiosurgery using the Gamma knife (Elekta AB). All technologies are not the same and neither doctors, patients, or insurance companies should assume that LINAC, Gamma knife, and Proton centers have equivalent risks or results. It is also likely that results reflect centers of experience, which are more likely to publish their results.

8. The risk of carotid closure is low even if the tumor envelops the artery. In the rare events where it occurs, collateral flow development during this slow process largely eliminates the risk of a delayed ischemic event.

9. Twenty years have been spent accumulating data related to single radiosurgery sessions including tumor response and cranial nerve effects. There is no compelling reason to revert to fractionated or hypofractionated radiation therapy using guidance technologies to improve the results. It would take a randomized prospective trial with likely 400 patients in each arm followed for 20 years to show benefit.

10. Level 1 Data is the goal of insurance companies and is used to deny care not to provide it. We cannot seek to obtain or even care about gathering Level I data for such rare and difficult tumors. It is Fake News.

11. Neurosurgeons who ignore their role in the treatment of such tumors do so at the risk that other fields will gladly pick up the torch. Ask any cardiac surgeon what happened to their field.

L. Dade Lunsford
Pittsburgh, Pennsylvania

There had been a lack of evidence-based guidelines to guide safe and effective practice of stereotactic radiosurgery (SRS) for World Health Organization (WHO) grade 1 cavernous sinus meningioma. The International Stereotactic Radiosurgery Society (ISRS) has put together a very comprehensive systematic review of the literature and has formulated this practice guideline. The inclusion of illustrations of post-SRS response for cavernous sinus tumors of different histology has further enhanced the usefulness of this guideline, which will be invaluable to neurosurgeons and radiation oncologists performing SRS for meningiomas. The efforts of the authors of this ISRS guideline are commendable.

Simon S. Lo
Seattle, Washington