Title

Stereotactic Radiosurgery for Intracranial Noncavernous Sinus Benign Meningioma: International Stereotactic Radiosurgery Society Systematic Review, Meta-Analysis and Practice Guideline

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The study has been partially presented as an oral presentation at a breakfast seminar at the 14th International Stereotactic Radiosurgery Society (ISRS) Congress held in Rio de Janeiro, Brasil, June 10, 2019.

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Stereotactic Radiosurgery for Intracranial Noncavernous Sinus Benign Meningioma: International Stereotactic Radiosurgery Society Systematic Review, Meta-Analysis and Practice Guideline

BACKGROUND: Stereotactic radiosurgery (SRS) for benign intracranial meningiomas is an established treatment.
OBJECTIVE: To summarize the literature and provide evidence-based practice guidelines on behalf of the International Stereotactic Radiosurgery Society (ISRS).
METHODS: Articles in English specific to SRS for benign intracranial meningioma, published from January 1964 to April 2018, were systematically reviewed. Three electronic databases, PubMed, EMBASE, and the Cochrane Central Register, were searched.
RESULTS: Out of the 2844 studies identified, 305 had a full text evaluation and 27 studies met the criteria to be included in this analysis. All but one were retrospective studies. The 10-yr local control (LC) rate ranged from 71% to 100%. The 10-yr progression-free-survival rate ranged from 55% to 97%. The prescription dose ranged typically between 12 and 15 Gy, delivered in a single fraction. Toxicity rate was generally low.
CONCLUSION: The current literature supporting SRS for benign intracranial meningioma lacks level I and II evidence. However, when summarizing the large number of level III studies, it is clear that SRS can be recommended as an effective evidence-based treatment option (recommendation level II) for grade 1 meningioma.

KEY WORDS: Radiosurgery, Multisession-radiosurgery, Fractionated radiosurgery, Hypofractionated stereotactic radiotherapy, Meningioma, Guidelines, Systematic review

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Meningioma is the most common primary intracranial tumor among adults, accounting for approximately 12% to 29% of all the cases. Meningiomas are mostly benign (WHO grade I) lesions, and atypical (WHO grade II) and malignant meningiomas (WHO grade III) are regarded as more aggressive variants.[1] This investigation focuses on WHO grade I meningiomas.

Despite their benign nature, the treatment of meningiomas can be challenging. Gross total resection (GTR) has traditionally represented the treatment of choice and it is potentially curative, although the complete removal of the lesion may be difficult when the tumor is close to and/or invades neural or vascular structures. In these situations, a subtotal removal is generally performed, albeit with lower long-term local control (LC) outcomes.[2,3] Based on the anatomic location, in particular the skull base, surgery may imply significant risks to the patient and cause serious harm.[2,4] For

ABBREVIATIONS: CI, confidence interval; **CS,** cavernous sinus; **CT,** computed tomography; **GTR,** gross total resection; **HSRT,** hypofractionated stereotactic radiotherapy; **ISRS,** International Stereotactic Radiosurgery Society; **LC,** local control; **MRI,** magnetic resonance imaging; **PFS,** progression-free-survival; **PRISMA,** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **SE,** standard error; **SRS,** stereotactic radiosurgery; **SRT,** stereotactic radiotherapy; **TV,** target volume

Supplemental digital content is available for this article at www.neurosurgery-online.com.

these surgically difficult cases, the treatment strategy has evolved to incorporate some form of radiation, not only as adjuvant or salvage therapy, but as the primary treatment often without tissue confirmation.[5-7] Radiation can be delivered with stereotactic precision as a single treatment using a stereotactic radiosurgery (SRS) technique, or as fully fractionated stereotactic radiotherapy (SRT) which is again based on stereotactic principles but typically delivered over 5 to 6 wk and a dose per fraction ranging from 1.8 to 3.0 Gy. With the advent of frameless image-guided SRS systems, there is the ability to deliver SRS in more than one fraction, which is known as hypofractionated stereotactic radiotherapy (HSRT), and typically HSRT refers to no more than 5 fractions and a dose per fraction ≥5 Gy.

On behalf of the International Stereotactic Radiosurgery Society (ISRS) Guideline Committee, this report summarizes the current literature specific to SRS outcomes for WHO Grade I intracranial meningioma, and to provide therapeutic guidelines. Cavernous sinus (CS) meningiomas have been excluded from this analysis as they were the subject of a previous ISRS guideline.[8]

METHODS

Article Selection

The ISRS clinical practice guideline taskforce conducted a systematic review of the literature specific to the management of intracranial meningioma with SRS, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (2009) and the Cochrane guidelines for systematic reviews of interventions.[9] Articles were included when inclusion criteria were met.

Inclusion Criteria

Retrospective and prospective studies reporting outcomes on adult patients with a radiological and/or pathological diagnosis of intracranial WHO grade I meningioma were included. In those series that included other grades of meningioma (WHO grade II and III), only those studies that segregated outcomes for the WHO grade I population were included. Similarly, those studies including CS meningioma were excluded, unless outcomes were segregated for non-CS meningioma. For series reporting outcomes without segregating the study population to non-CS patients and CS patients, an exception was made, provided that the proportion of CS patients included did not exceed 30% to 40% of the overall population. A minimum follow-up period of 3 yr was deemed mandatory for the analysis of LC and progression-free-survival (PFS); series with a mean/median follow-up period lower than 36 mo have been considered if specified the number of patients for which a longer than 3 yr follow-up is available.

Studies which included re-irradiated patients, or whose population amounted to less than 10 patients, were also excluded. SRS and HSRT, delivered over 2 to 5 fractions, were permitted. Lastly, patients who had been treated with primary or adjuvant/salvage SRS were included.

Objectives

The primary objective of the study was to define the efficacy of SRS in the treatment of intracranial WHO grade I meningioma (excluding CS lesions). The primary outcomes analyzed were rates of LC, PFS, and overall survival.

Secondary objectives included analyses of symptoms-control, radiation-induced toxicity, and prognostic factors.

Search Strategy

The Medline, Embase, and Cochrane database were searched for English abstracts and keywords of relevant studies published until June 6, 2018. The details of the search strategy are listed in **Table**, **Supplemental Digital Content 1**.

Exclusion criteria have been recorded and listed in Figure 1.

Data Extraction

The extracted data include information on study design, follow-up interval, patient's demographic features, tumor characteristics, treatment parameters (including primary adjuvant and salvage setting), outcomes, and prognostic factors.

Risk-of-Bias Assessment

There is no single recommended instrument to assess the risk of bias for systematic reviews that includes both prospective and retrospective observational studies. We chose to evaluate the risk of bias by using a previously published system based on a 10-item assessment (see **Table**, **Supplemental Digital Content 2**).[7]

The system was developed to evaluate the kind of bias and the completeness of information. Particularly, items 1 and 2 assess the selection bias, items 3 to 5 the reporting bias, item 6 the attrition bias, and items 7 to 10 assess the extensiveness of information on treatments and outcomes. Specifically, an affirmative answer, "yes," indicates a low risk of bias, while a negative answer, "no," a high risk. Unclear or unknown risks are indicated by the definition "unclear."

Ranking the Evidence Quality

The evidence quality was ranked by applying an evidence hierarchy developed by the ISRS Guidelines Committee for a number of studies: diagnostic, prognostic, therapeutic, and decision modeling. The method used to assess the quality of the evidence is exemplified in this link: https://www.cns.org/guidelines/guideline-development-methodology.

Strength of Recommendation Rating Scheme

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

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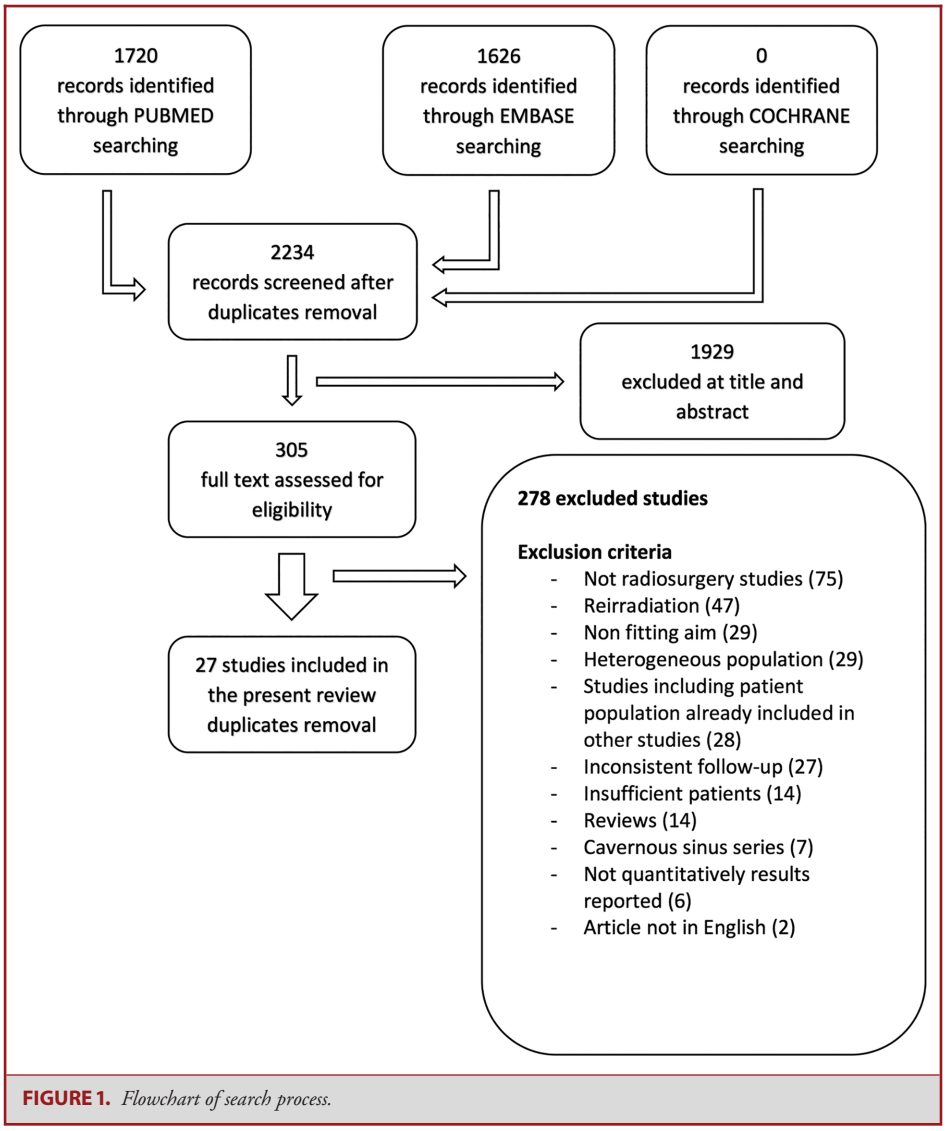

FIGURE 1. *Flowchart of search process.*

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

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

Statistical Methods

The 3-yr, 5-yr, and 10-yr rates and the respective CI and/or standard errors (SE) for efficacy end points were extracted and reported from each study, where available or deducible.

The percentage of patients with symptom control and the percentage of patients suffering at least from one toxicity (together with the 95% CI) were also extracted or calculated. The Freemen-Tukey double arcsine transformation was performed to obtain the overall estimates, and the DerSimonian-Laird random effect model has been applied to calculate the weighted pooled estimate. The overall estimate was back-transformed.

The STATA software, version 14.3 (StataCorp), has been used to analyze the data.

RESULTS

Selection of the Studies

The PubMed, Embase, and Cochran searches identified 2844 studies. After the removal of duplicates, 2233 papers remained, out of which 1927 were excluded upon title and abstract evaluation. Following a full text scrutiny of the remaining 305 studies, 27 studies[10-36] were deemed to have met the inclusion criteria and selected for this review and summarized in Figure 1. One study was prospective,[19] in 4 studies the study design was unclear,[10,21,24,32] and the remaining studies were retrospective.

TABLE 1. Studies, Tumors, and Treatments Features

Author/year	Level of evidence	Period	Study design	Patients age (range)	Follow-up, months (range)	Analyzed patients (present review) (#)	Treatment type, N (%)			Device	Tumor volume (cm^3) (range)	SRS or HSRT	Prescription dose (Gy) (range)	Max dose (Gy)	Isodose (%) (range)
							Primary	Adjuvant	Salvage						
Abdelaziz/2011[10]	III	2004-2006	Retrosp mono	46 (M) (17-67)	60 (M) (36-70)	23	23 (77.7)	7 (23.3)	0	LINAC	6.4 (M) (1.3-15.0)	SRS	11.0 (M) (8.0-14.0)[a]	15 (M)	80 (M) (75-90)
Aichholzer/2000[11]	III	1992-1995	Retrosp mono	59 (m) (35-81)	48 (m) (36-76)[a]	15	15 (100.0)	0	0	GK	n/a	SRS	17.3 (n/a) (13.0-25.0)	n/a	50 (n/a) (40-70)
Azar/2016[12]	III	2003-2012	Retrosp mono	59 (m) (24-94)	58 (m) (sd 36)	122	n/a	n/a	n/a	GK	12.24 (m) (sd 9.3)	SRS	13 (m) (sd 1)	22 (m)	59.5 (n/a)
Bir/2014[13]	III	2000-2013	Retrosp mono	57 (M) (27-101)	60 (M) (6-156)	136	68 (50.0)	n/a	n/a	GK	5.4 (m) (0.4-18.0)	SRS	14 (m) (12.0-30.0)	27 (m) (10-44)	50 (m) (50-80)
Chung/2009[14]	III	1997-2006	Retrosp mono	55 (m) (26-78)	42 (m) (12-119)	80	80 (100.0)	0	0	GK	5.6 (m) (0.5-16.8)	SRS	14.6 (m) (10.0-20.0)	n/a	50 (M) (45-55)
Davidson/2007[15]	III	1994-2004	Retrosp mono	55 (M) (22-73)	81 (M) (30-141)	36	–	34 (94.4)	2 (5.6)	GK	4.1 (M) (0.8-20.0)	SRS	16.0 (M) (15.0-16.0)	32 M	n/a
Demiral/2016[16]	III	2011-2016	Retrosp mono	40 (M) (24-77)	53 (M) (36-63)	19	14 (73.6)	n/a	n/a	LINAC	26 (M) (4-103)	HSRT	25/5 fr (all)	n/a	85-95
DiBiase/2004[17]	III	1992-2000	Retrosp mono	57 (M) (8-83)	54 (M) (4-126)	137	85 (62.0)	52 (38.0)	–	GK	4.5 (M) (0.3-80.0)	SRS	14.0 (M) (4.0-25.0)	n/a	50
El-Khatib/2015 [18]	III	1990-2007	Retrosp mono	52 (M) (9.7-82.4)	144 (M) (61-259)	148	88 (52.4)	n/a	n/a	LINAC	4.7 (M) (0.2-32.8)	SRS	12 (M) (7-20)	24 (M)	65 (54-85)
Feigl/2007 [19]	III	1999-2004	Prosp multi	58 (m) (9-81)	24 (m) (3-67)	211	88 (41.7)	123 (58.3)	0	GK	6.5 (m) (0.1-48.3)	SRS	13.6 (m) (10.0-18.0)	n/a	51 (m)
Han/2017[20]	III	2004-2015	Retrosp mono	64.5 (M) (27-86)	53.9 (M) (12-128)	70	48 (68.6)	n/a	n/a	GK	15.2 (M) (10.3-48.3) 21 (M) (10.2-54.7)	42 pts SRS 28 pts HSRT	12 (M) (8-14) 15/2fr (M) 18/3fr (M) 18/4fr (M)	n/a	50 (M)
Hasegawa/2011[21]	III	1991-2008	Retrosp mono	57 (M) (23-80)	72 (M) (4-184)	112	46 (41.1)	66 (59.9)	0	GK	7.9 (M) (0.2-62.7)	SRS	16.0 (M) (10.0-20.4)	30 (M)	n/a
Hasegawa/2018[22]	III	1990-2014	Retrosp mono	71 (M) (65-83)	52 (M) (7-195)	67	39 (68)	n/a	n/a	GK	4.9 (M) (0.7-22.9)	SRS	16 (M) (12-18)	n/a	n/a
Jo/2011[23]	III	1996-2008	Retrosp mono	55 (m) (27-83)	63 (m) (24-110)	69	n/a	n/a	n/a	GK	3.0 (m) (0.2-10.4)#	SRS	14.5 (m) (12.0-20.0)	n/a	n/a
Kalogeridi/2010[24]	III	2000-2004	Retrosp mono	66 (M) (35-84)	75 (50-99)[a]	14	12 (85.7)	2 (14.3)	0	LINAC	6 (M)	SRS	(12.0-15.5)	n/a	n/a
Kim/2017[25]	III	1998-2013	Retrosp mono	50 (m) (15-74)	68 (M) (3-195)	89	58 (65)	n/a	n/a	GK	6.7 (m) (0.5-46.3)	SRS	13.2 (m) (8.5-17)	n/a	50 (M) (48-60)
Kondziolka/2008[26]	III	Uk	Retrosp mono	57 (m)	48 (m)	488	488	0	0	GK	7.4 (m)	SRS	14.0 (m)	28 (m)	50 (d)
Kreil/2005[27]	III	1992-1999	Retrosp mono	57 (M) (10-81)	95 (M) (60-144)	200	101 (50.5)	n/a	n/a	GK	6.5 (M) (0.4-89.9)	SRS	12 (M) (7.0-25.0)	27 (M)	n/a
Lee/2016[28]	III	2000-2012	Retrosp mono	52 (m) (21-70)	46.1 (m) (12-120)	113	113 (100)	0	0	GK	0.5 (m) (0.12-0.98)	SRS	13.3 (m) (10-20)	25 (m)	50 (m) (40-60)
Manabe/2017[29]	III	2005-2015	Retrosp mono	70 (M) (33-92)	49 (M) (7-138)	41	41	0	0	CK	10.4 (M) (1.7-29.3) 4.6 SRS (M) 11.3 MRS	9 pts SRS 32 pts HSRT	17 (M) (13-20) 25 (M) 14-38/2-10fr	n/a	(61-88) (44-83)
Mansouri/2015[30]	III	2005-2012	Retrosp mono	58.6 (m) (24-90)	36.2 (M) (24-85)	75	54 (72)	21 (28)	0	GK	5.2 (M) (0.7-25.8)	SRS	13 (m) (12-16)	28 (m)	48 (m) (20-80)

TABLE 1. Continued

Author/year	Level of evidence	Period	Study design	Patients age (range)	Follow-up, months (range)	Analyzed patients (present review) (#)	Treatment type, N (%)			Device	Tumor volume (cm^3) (range)	SRS or HSRT	Prescription dose (Gy) (range)	Max dose (Gy)	Isodose (%) (range)
							Primary	Adjuvant	Salvage						
Marchetti/2016[31]	III	2004-2013	Retrosp mono	52 (M) (18-80)	32 (M) (12-113)	143	71 (50)	n/a	n/a	CK	7.6 (M) (0.1-126.3)	HSRT	25 (M) 14-25/3-5fr	31 (M)	80 (M) (65-86)
Massager/2013[32]	III	1999-2007	Retrosp mono	53 (M) (10-88)	84 (M) (60-138)	120	n/a	n/a	n/a	GK	3.8 (M) (0.2-13.5)	SRS	13.0 (M) (12.0-16.0)	n/a	n/a
Pollock/2012[33]	III	1990-2008	Retrosp mono	57 (M) (13-90)	60 (M) (6-234)	416	252 (60.6)	n/a	n/a	GK	7.3 (M) (0.3-48.6)#	SRS	16.0 (M) (12.0-20.0) 15 vs 18 (post and pre 1998)	32 (M)	n/a
Ryttlefors/2016[34]	III		Retrosp mono	52 (m) (34-66)	139 (M) (73-192)	19	4 (21)	8 (42)	7 (37)	Proton	(2-53)	HSRT	24/4fr (all)	n/a	n/a
Sheehan/2014[35]	III	1988-2011	Retrosp multi	56 (M) (8-90)	67 (M) (6-216)[a]	575	n/a	n/a	n/a	GK	6.7 (M) (0.1-54.8)	SRS	13.0 (M) (5.0-30.0)[b]	28 (M)	n/a
Zada/2010[36]	III	1996-2004	Retrosp mono	58 (m) (12-89)	75 (M) (4-146)	116	44 (37.9)	72 (62.1)	0	GK	3.8 (M) (0.1-31.1)	SRS	16.0 (M) (14.0-17.0)	n/a	50 (all)

Acronym and symbol: # = treatment volume; N/A = not available; GK = Gamma Knife; CK = CyberKnife; multi = multicentric; mono = monocentric; retrosp = retrospective; prosp = prospective; M = median; m = mean; d = mode.

[a]Data on patients analyzed in the article.

Two studies were multicenter,[19,35] while the remaining were single-center institutional series.

Risk-of-Bias Assessment

Based on the established risk-of-bias assessment method, none of the analyzed studies fulfill the criteria for low risk of bias, according to the defined 4 sections (selection bias, reporting bias, attrition bias, extensiveness of information on intervention analyzed). Four studies could be considered at low risk for selection bias, as they enrolled patients in a consecutive manner and reported the reasons to exclude some patients from the study.[19,24,25,28] Five studies were considered at low risk for reporting bias.[15,30,31,33,36] A total of 14 studies should be considered at low risk of attrition bias.[10,11,13-15,17,19-21,23-25,27,28] All but one[35] of the series included was at risk of bias with respect to the reporting of the results. Details about the Risk-of-Bias evaluation are reported in **Table**, **Supplemental Digital Content 3**.

Patient and Tumor Characteristics

From the reviewed literature summarized in Table 1, a total of 3654 patients (3750 tumors) were included. The median follow-up was 60 mo. The mean patient age at the time of treatment ranged from 40 to 71 (median, 57 yr). The percentage of male patients across studies ranged from 11% to 41% (median, 26%). The analysis includes WHO grade I meningiomas treated with SRS and HSRT; the grade was based on pathological confirmation or based on radiological assessment. A single study included grade II and II meningiomas; however, WHO grade I tumors were reported separately and, as a result, they have been than included in this analysis.[19] The tumor site distribution is represented in Table 2. The overall tumor volume ranged from 0.5 to 26 cc (median, 6.4 cc), and ranged from 0.5 to 15.2 cc (median, 5.6 cc) in the SRS series and from 7.6 to 26 cc (median, 16.2 cc) in the HSRT series.

Tumor Control and PFS Rates

A total of 16 studies provide data specific to LC, 5 of which, evaluating 662 patients, reported a 10-yr LC rate ranging from 71% to 100% (median, 94.2%).[15,21,23,26,33] Eight studies, including more than 783 patients, reported a 5-yr posttreatment LC rate ranging from 85% the 100% (median, 93.8%).[14,15,21,23,24,26,29,33] Ten studies, evaluating more than 750 patients, reported LC rates ranging from 52% to 100% based on the last follow-up.[10,11,16,20,25,26,28,30,32,34]

PFS was reported in 15 studies. The longest reported observation period was 15 yr in one study with a PFS of 89%.[18] Eight- to ten-year PFS rates were reported in 10 studies[12,13,18,21,22,25,27,31,35,36] that evaluated more than 1146 patients, with a PFS rate ranging from 55% to 97% (median, 85.0%). Four- to five-year PFS rates ranged from 74% to 99% (median, 89.4%) in 14 studies, based on more than 1057 patients.[12,13,16-22,25,27,29,31,36]

TABLE 2. The Meningiomas Sites Are Here Described

Author/year	Site of meningiomas, N (%)			
	Skull base and posterior cranial fossa (%)	Supratentorial (%)	Falco-tentorial (including parasagittal and torcular) (%)	Miscellaneous (including intraventricular) (%)
Abdelaziz/2011[10]	22 (73.3)	–	8 (26.7)	–
Aichholzer/2000[11]	39 (86)[a]	–	4(8)[a]	3 (6)[a]
Azar/2016[12]	122 (100.0)	–	–	–
Bir/2014[13]	136 (100.0)	–	–	
Chung/2009[14]	5 (6.1)	21 (25.6)	43 (52.4)	13 (15.9)
Davidson/2007[15]	36 (100.0)	–	–	–
Demiral/2016[16]	19 (100.0)	–	–	–
DiBiase/2004[17]	92 (66.2)	25 (18.0)	22 (15.8)	–
El-Khatib/2015[18]	111 (66.1)	18 (10.7)	39 (23.2)	–
Feigl/2007[19]	170 (70.0)	20 (8.2)	48 (19.8)	5 (2.0)
Han/2017[20]	40	N/A	N/A	N/A
Hasegawa/2011[21]	7 (5.6)	23 (18.4)	95 (76.0)	–
Hasegawa/2018[22]	44 (63.7)	12 (17.3)	12 (17.3)	1 (1.7)
Jo/2011[23]	12 (17.4)	15 (21.7)	34 (43.3)	8 (11.6)
Kalogeridi/2010[24]	7 (50.0)	7 (50.0)	–	–
Kim/2017[25]	89 (100.0)	–	–	–
Kondziolka/2008[26]	691 (66.1)[a]	126 (12.1)[a]	206 (19.7)[a]	22 (2.1)[a]
Kreil/2005[27]	193 (96.5)	–	–	7 (3.5)
Lee/2016[28]	9 (8.0)	44 (38.9)	60 (53.1)	0
Manabe/2017[29]	14 (34.2)	11 (26.8)	15 (36.6)	1 (2.4)
Mansouri/2015[30]	40 (53.3)	14 (18.7)	20 (26.7)	1 (1.3)
Marchetti/2016[31]	143 (100.0)	–	–	–
Massager/2013[32]	N/A	N/A	N/A	N/A
Pollock/2012[33]	303 (72.8)	22 (5.3)	91 (21.9)	–
Ryttlefors/2016[34]	19 (100.0)	–	–	–
Sheehan/2014[35]	575 (100.0)	–	–	–
Zada/2010[36]	81 (59,6)	38 (27.9)	16 (11,8)	1 (0.7)

[a]All the reported tumors, including WHO grade > 1 and cavernous sinus meningiomas. N/A not available unknown.

Amongst those reporting predictive factors, the most common factors associated with tumor control were smaller tumor volume[12,18,26,33] and patient age (lower than 65).[12,21,36]

The impact of tumor location on the tumor control was investigated by 4 studies.[18,20,22,33] Two out of these studies[22,33] suggest that parafalcine, parasagittal, and convexity locations are significant negative prognostic factors in terms of tumor control, while other 2 studies[18,20] did not observe statistical significance.

Tumor-control rates and the PFS are summarized in Table 3.

Treatment Features and Dose

A total of 22 papers reported specifically on single-fraction SRS (3458 tumors have been included),[10-15,17-19,21-28,30,32,33,35,36] one of which included staged SRS (8/200 total treatments).[27] Three studies (based on 181 tumors) reported outcomes specific to HSRT.[16,31,34] Two studies included both SRS and HSRT treatments; in these studies, 51 tumors had SRS and 60 tumors had HSRT.[20,29] The Gamma Knife (Elekta AB) was the reference device in 20 studies (3316 tumors),[11-15,17,19-23,25-28,30,32,33,35,36] the LINAC in 4 (231 tumors),[10,16,18,24] the CyberKnife (Accuray) in 2 (184 tumors),[29,31] and proton SRS in 1 study (19 tumors).[34]

The SRS prescription dose ranged from 11 to 17 Gy (median, 14 Gy), and the prescription isodose line ranged from 20% to 90% (median, 50%). The maximum point dose ranged from 15 to 32 Gy (median, 27 Gy). Doses varied widely across all analyzed papers; older series generally included treatments whose total dose was higher than in more recent series (15 to 12 Gy, marginal).

The most common schedule for HSRT was 25 Gy in 5 fractions.[16,29,31] The observed HSRT schedules ranged from 14 to 30 Gy delivered in 2 to 5 fractions. The prescription isodose line ranged from 44% to the 95% isodose line.

Primary, Adjuvant, or Salvage Therapy

Approximately half of the study population in this analysis underwent SRS as primary treatment. Two studies found that

TABLE 3. Local Control and Progression-Free-Survival Rates

Author, yr	3 yr		5 yr		10 yr		Last clinical follow-up	
	Analyzed patient (#)	Rate (95% CI)	Analyzed patient (#)	Rate (95% CI)	Analyzed patient (#)	Rate (95% CI)	Analyzed patient (#)	Rate (95% CI)
Local control								
Abdelaziz/2011[10]	–	–	–	–	–	–	23	95.7
Aichholzer/2000[11]	–	–	–	–	–	–	15	93.3
Chung/2009[14]	–	–	80	91.6	–	–	–	–
Davidson/2007[15]	–	–	36	100	36	94.7 (68.1-99.2)	–	–
Demiral/2016[16]	–	–	–	–	–	–	–	89.4
Han/2017[20]	–	–	–	–	–	–	–	90 (5 yr)
Hasegawa/2011[21]	–	–	119	87	119	71	–	–
Jo/2011[23]	69	100	69	100	69	100	–	–
Kalogeridi/2010[24]	14	100	14	100	–	–	14	100.0
Kim/2017[25]	–	–	–	–	–	–	–	94.4
Kondziolka/2008[26]	–	–	49	94b	22	95	488	97 (median 4 yr)
Lee/2016[28]	–	–	–	–	–	–	104	92.1
Manabe/2017[29]	–	–	–	85	–	–	–	–
Mansouri/2015[30]	–	–	–	–	–	–	–	52 (3D) 92 (2D)
Massager/2013[32]	–	–	–	–	–	–	120	92.5
Pollock/2012[33]	–	–	416	96.0	416	89	–	–
Ryttlefors/2016[34]	–	–	–	–	–	–	–	89.5 at least 5 yr
Progression-free survival								
Azar/2016[12]	–	82.7	–	74.1	–	56.6	–	–
Bir/2014[13]	136	98.0	136	95.0	136	85.0	–	–
Demiral/2016[16]	–	–	–	89.4c	–	–	–	–
DiBiase/2004[17]	–	–	137	86.2	–	–	–	–
El-Khatib/2015[18]	–	–	–	92.0	–	89	–	89 (15 yr)
Feigl/2007[19]	–	–	211	86.3[a]	–	–	–	–
Han/2017[20]	–	–	–	92.9 HSRT 88.1 SRS	–	–	–	–
Hasegawa/2011[21]	–	–	108	78.0	108	55.0	–	–
Hasegawa/2018[22]	–	–	29	86	11	72	–	–
Kim/2017[25]	–	–	–	94.7	–	88.9	–	–
Kreil/2005[27]	200	98.5 (95.4-99.5)	200	98.5 (95.4-99.5)	200	97.2	–	–
Manabe/2017[29]	–	–	–	86	–	–	–	–
Marchetti/2016[31]	120	100	42	93 (81-97)	5	90b (78-96)	–	–
Sheehan/2014[35]	–	–	–	–	575	80.9 (73.3-86.5)	–	–
Zada/2010[36]	116	100.0	116	98.9	116	84.0	–	–

a = 4 yr rate; b = 8 yr rate.

previous surgery was associated with worse tumor LC.[21,22] Similarly, El-Khatib et al[18] reported better PFS at 5, 10, and 15 yr when SRS was performed as a primary treatment as opposed to an adjuvant or salvage indication. From the Mayo clinic, Pollock et al[33] also reported prior surgery (hazard ratio: 6.9, $P = .002$) to be a negative risk factor in terms of local tumor control, as did Sheehan et al,[35] who concluded that more than one prior surgery significantly increased the likelihood of tumor progression after SRS. However, a recent series by Kim et al[25] failed to detect any relationship with prior surgery and LC following SRS.

Single-Session or Fractionated Treatments

Single-session SRS was considered the reference treatment (level II recommendation) as an established practice, with consistent reports of LC with mature follow-up.[10-15,17-19,21-28,30,32,33,35,36] Five series evaluated HSRT

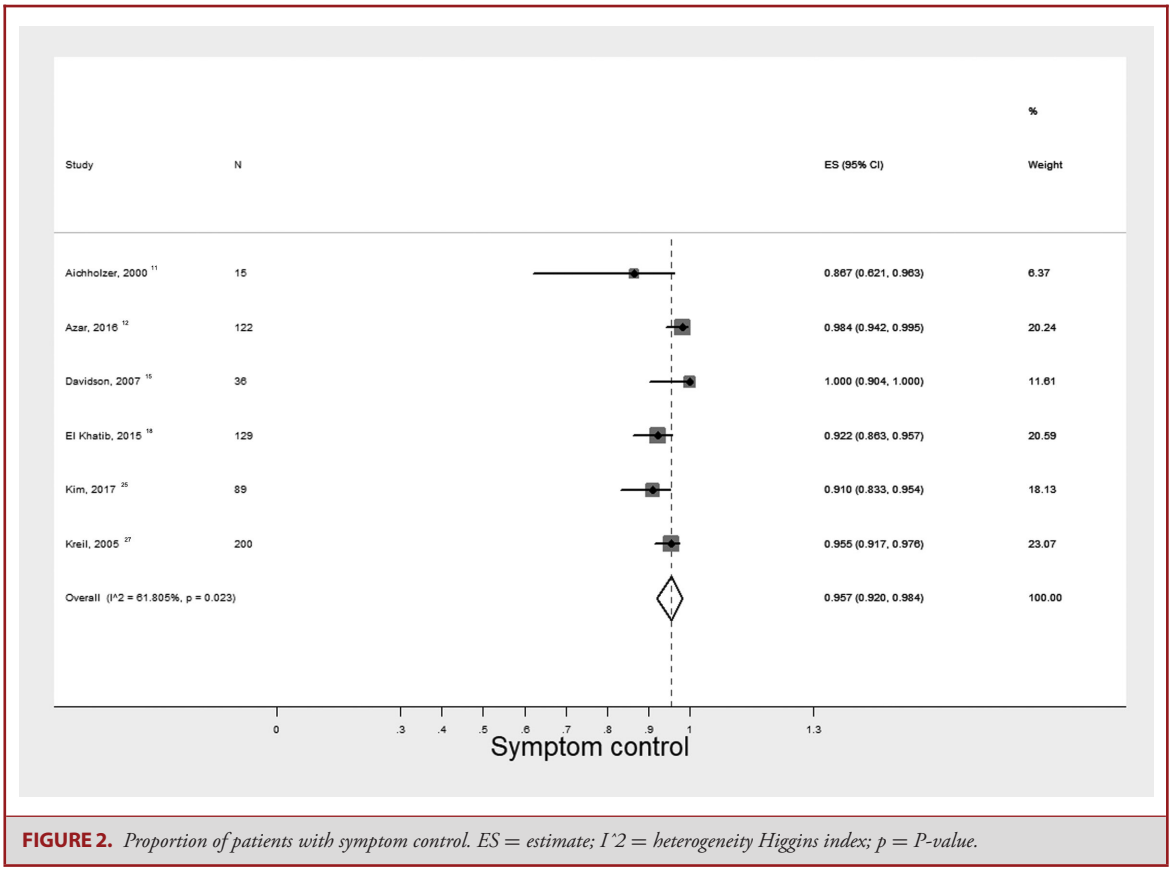

FIGURE 2. *Proportion of patients with symptom control. ES = estimate; I^2 = heterogeneity Higgins index; p = P-value.*

and, although the data are limited, similar results were observed.[16,20,29,31,34]

Despite the limited number of the analyzed patients, 2 studies comparing SRS with HSRT would suggest a potential role of HSRT for large lesions.[20,29]

Four studies, all analyzing SRS, found that a higher tumor volume is a negative prognostic factor in terms of tumor control.[12,18,26,33] One of the few studies on HSRT (120 patients with follow-up longer than 3 yr) did not show any correlation between tumor volume and PFS.[31]

Imaging and Contouring Techniques

The oldest series included treatments based on computed tomography (CT) images. In more modern series, the target and the critical structures are additionally defined using magnetic resonance imaging (MRI) scans. Specific to the MRI protocol, the T1 axial contrast-enhanced MRI was the most used sequence to define the target volume (TV). The TV was contoured according to the contrast enhancement without any further margin in most of the series. A T2 fast spin echo with a slice thickness of 1 to 1.5 mm could be recommended for inner-ear and/or cranial nerve definition. Two studies specifically debated the inclusion of the dural tail and concluded that it should be included in the TV, although without any specific analysis to support such practice.[11,17]

Neurological Outcomes and Adverse Events

Eight studies suggest a post-SRS neurological deterioration rate ranging from 0% to 13.3% (median, 7.4%).[11,12,15,16,18,25,27,31] The meta-analysis, possible for 6 out of these studies,[11,12,15,16,18,25,27] suggests an overall symptoms control rate of 95.1% (95% CI: 92.1%-97.5%); an estimate for the relative frequency of patients with symptom control was obtained, with high heterogeneity among studies (I2 = 53.8%) (see Figure 2).

In general, toxicity rates ranged from 2.5% to 34.6% (median, 8.0%) in 13 papers.[11,13-17,19-22,27,30,33] A single study reported 2 cases of grade 4 toxicity (system of reporting not mentioned).[29] The meta-analysis was possible for 11 out of these studies[11,13-15,17,19,21,27,30,33,36]; the data showed an overall relative frequency of patients with toxicity of 11.0% (95% CI: 6.4%-16.5%) with a high heterogeneity (I2 = 88.1%) among studies (Figure 3).

Possible prognostic factors for a negative clinical outcome were higher marginal dose[22] and larger volumes.[33] Two studies[20,33] suggest that the postradiosurgery edema rate may be related to

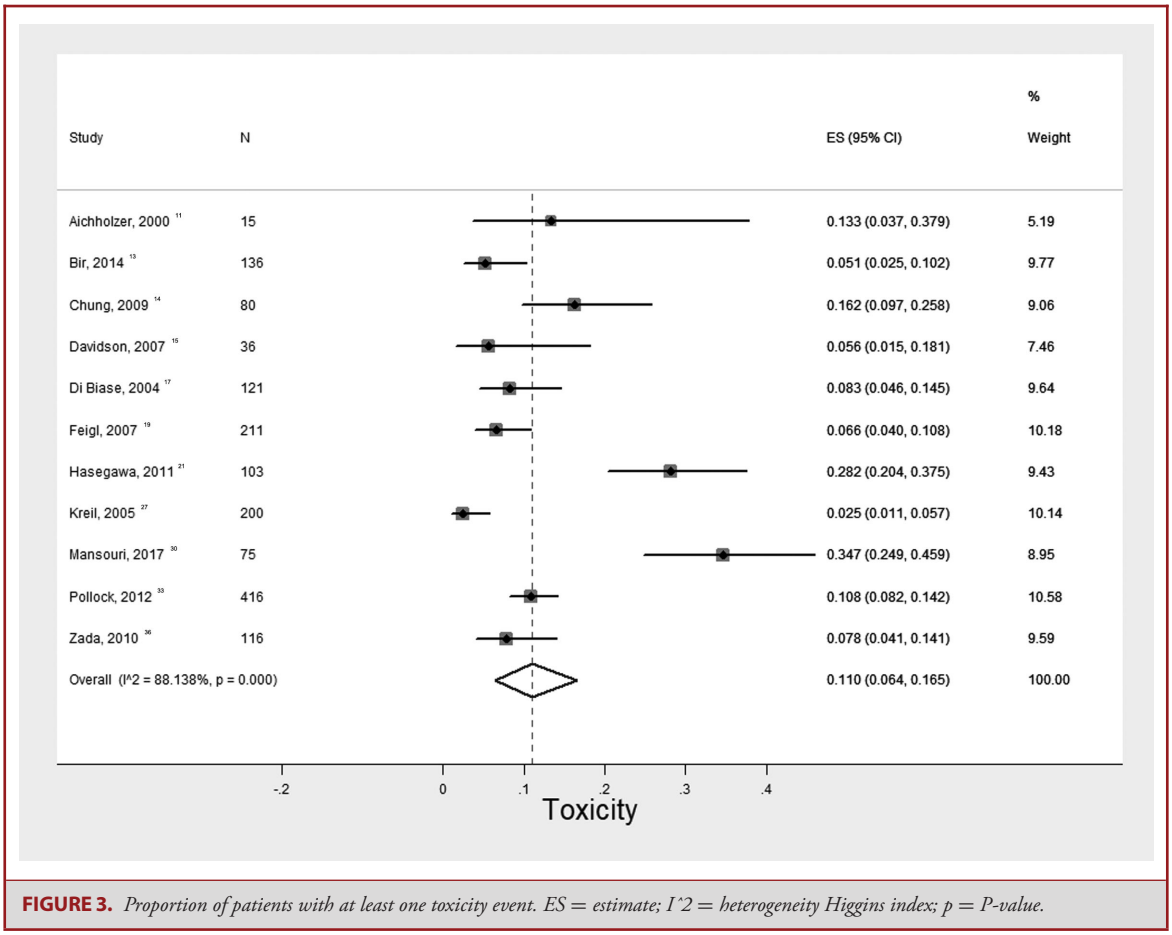

FIGURE 3. *Proportion of patients with at least one toxicity event. ES = estimate; I^2 = heterogeneity Higgins index; p = P-value.*

the parafalcine, parasagittal, and convexity locations, while 2 studies[28,30] failed to observe a correlation between tumor location and clinical or radiological toxicity.

The clinical and toxicity data are summarized in Tables 4 and 5.

DISCUSSION

The results of this systematic review support the effectiveness of SRS with respect to LC for WHO grade I meningioma. The 5-yr PFS ranged from 85% to 100% (median, 89%) and the 10-yr PFS ranged from 53% to 100% (median, 85%). These data are consistent with what we observe in the surgical literature[37] and may further explain the reason why SRS is being increasingly used as the primary therapeutic modality for meningioma.

Regarding the dose, the most recent data show that a marginal dose ranging from 15 to 12 Gy is generally sufficient with respect to durable LC.[27,38]

With regards to HSRT, the literature lacks the mature long-term outcomes to draw any firm conclusions; however, the preliminary data summarized in this review suggest a potential role of such a technique in selected cases, and the most common fractionation schedule is 25 Gy in 5 fractions.

Whether SRS as a primary treatment is preferable to adjuvant SRS remains to be confirmed. However, the evidence suggests that previous surgery may adversely affect tumor control.[18,21,22,33,35] This could be related to a more complex definition of the target volume due to the complexity of the postoperative radiological images and/or to a potentially more aggressive inherent biology, given that patients required surgery as upfront treatment without a GTR possible. There is no evidence that adjuvant SRS may yield better results than salvage SRS, or vice versa. The choice has been largely been based on the clinician's or institution's preference and by taking into account a variety of factors such as tumor volume and location, previous surgery, clinical condition, age, etc. The specifics with respect to decision making were not stipulated in the relevant series and are beyond the scope of this review.

The issue regarding optimal imaging has not been defined yet; it is very important to establish a common strategy to delineate the TV and critical structures. Most studies define the TV as the contrast-enhanced tumor without margins. The role of biological

TABLE 4. Treatment Response in Terms of Symptom Control

		Symptom control		
Author, publication year	SRS or HSRT	Analyzed patients (#)	Worsened patients # (%)	Patients with symptom control # (%)
Aichholzer/2000[11]	SRS	15	2 (13.3)	13 (86.7)
Azar/2016[12]	SRS	122	2 (1.6)	120 (98.4)
Davidson/2007[15]	SRS	36	0 (0.0)	36 (100.0)
Demiral/2016[16]	HSRT	19	2 (10.6)	17 (89.4)
El-Khatib/2015[18]	SRS	129	10 (7.8)	119 (92.3)
Kim/2017[25]	SRS	–	8 (9)	81 (91)
Kreil/2005[27]	SRS	200	9 (4.5)	191 (95.5)
Marchetti/2016[31]	HSRT	143	10 (7.4)	133 (82.6)

TABLE 5. Treatment-Related Toxicity Rates

			Toxicity	
Author/publication year	Analyzed period	SRS or HSRT	Analyzed patients #	Patients with at least one toxicity event # (%)
Aichholzer/2000[11]	1992-1995	SRS	15	2 (13.3)
Bir/2014[13]	2000-2013	SRS	136	7 (5.1)
Chung/2009[14]	1997-2006	SRS	80	13 (16.3)
Davidson/2007[15]	1994-2004	SRS	36	2 (5.6)
Demiral/2016[16]	2011-2016	HSRT	19	4 (21) edema
DiBiase/2004[17]	1992-2000	SRS	121	10 (8.3)
Feigl/2007[19]	1999-2004	SRS	211	14 (6.6)
Han/2017[20]	2004-2015	SRS	70	14 pts SRS
		HSRT		2 pts HSRT
Hasegawa/2011[21]	1991-2008	SRS	103	29 (28.2)
Hasegawa/2018[22]	1990-2014	SRS		7 pts edema/3 symtomatic
Kreil/2005[27]	1992-1999	SRS	200	5 (2.5)
Manabe/2017[29]	2005-2015	SRS		2 pts grade 4 toxicity
		HSRT		
Mansouri/2015[30]	2005-2012	SRS	75	26 (34.6)
Marchetti/2016[31]	2004-2013	HSRT	143	0 > grade 2
Pollock/2012[33]	1990-2008	SRS	416	45 (10.8)
Ryttlefors/2016[34]	–	HSRT		1 pt edema
Zada/2010[36]	1996-2004	SRS	116	9 (7.8)

imaging (CT/MRI positron emission tomography) requires a more in-depth investigation as well.

Finally, regarding clinical outcome and toxicity, it is well known that specific treatment-related risks are often closely linked to the tumor location. For example, skull base meningioma often involves cranial nerves, and sparing them becomes challenging both in terms of surgery and SRS. Parasagittal meningiomas are also associated with an increased risk of post-SRS edema, and there is a lack of outcome data co-relating the risk of edema with dose fractionation and volume. The results on neurological toxicity from this review suggest a low risk of neurological deterioration (median 7.4%) and a low rate of serious adverse events (median 8.0%).

The role of the tumor location in term of both tumor control and clinical outcome is also of importance and requires further investigation.

Cognitive status and quality-of-life were not analyzed in the literature reviewed and are an active area of investigation. A summary of recommendations based on this review of the evidence as endorsed by the ISRS are provided in Table 6.

Key Areas for Future Investigation

- Although SRS in the treatment of intracranial benign meningioma is being increasingly used, the literature lacks class I and II evidence. Higher-level evidence is needed, particularly in regards to comparative analysis of SRS, HSRT, intensity modulated radiation therapy, charged particle radiation, and the various surgical techniques, in order to help clinicians make optimal therapeutic decisions.
- The timing of SRS (primary, adjuvant, or as salvage treatment) requires further investigation.

TABLE 6. Summary of the ISRS Recommendations for SRS and Meningioma

Recommendations level
Recommendation level II. SRS may be proposed as a primary treatment modality for an asymptomatic or mildly symptomatic meningioma, and should be considered when a complete surgical excision cannot be achieved or is not amenable
Recommendation level II. After surgery, when a residual tumor is not evident or is minimal, a wait-and-scan approach appears to be reasonable with a regular radiological follow-up. At the time of recurrence or progression, SRS should be taken into consideration as a treatment modality. Some studies suggest that the recurrence/progression rate is lower when SRS is delivered as the primary treatment as compared to an adjuvant treatment and this remains to be confirmed.
Recommendation level III. Single-fraction SRS with a dose of 12 to 15 Gy appears to be sufficient to manage benign intracranial meningioma. A prescription dose of at least 14 Gy would be advisable.
Recommendation level III. HSRT may be considered for the treatment of large or/and critically located meningioma. Optimal practice has yet to be defined; however, 25 Gy in 5 fractions is a common approach.
Recommendation level III. SRS generally entails a low risk of neurological deterioration. Patients may experience a clinical improvement without tumor shrinkage.

- Before HSRT can be recommended as a standard of care, mature follow-up of existing series is needed and ideally comparative clinical trials, especially for large or meningioma located in critical locations where SRS is limited by dose tolerances.
- Further research as to the ideal MR sequence to define the TV, including the dural tail, and the incorporation of multimodal imaging, including biological imaging, is needed.
- While there is consensus on the prescription dose for SRS, the best treatment schedule, dose-per-fraction, and total dose for HSRT require further investigations.

Study Limitations

The main limitations with respect to the conclusions from this systematic review lie in the lack of strong evidence and, in general, the lack of a common terminology with respect to endpoints, as pointed out by the risk-of-bias assessment.

The limited number of studies reporting the CI and/or the number of patients at risk at any given time limited the possibility of a meta-analysis about the efficacy.

Randomized controlled trials would be recommended; on the other hand, such studies are unlikely to be performed given current practice patterns, funding constraints, and clinical equipoise.

CONCLUSION

SRS has traditionally been considered to be an adjuvant treatment modality in case of remnants or recurrent tumors, or as primary treatment for patients who are not surgically amenable. Regardless of the indication, SRS represents an important treatment option for most benign intracranial meningiomas.

Given the strong consensus of class III evidence studies with favorable outcomes, today SRS can be considered a primary treatment in many cases (recommendation level II). Tumor control rates are generally high, with rare events of post-SRS deterioration. However, due to the lack of class level I and II evidence, further investigation with longer periods of observation and larger, multiinstitutional series are needed. Finally, the development of common terminology criteria and reporting methodology is desirable to ensure consistency in the interpretation of the evidence.

Disclosures

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Disclaimer

These consensus reviews 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 Stereotactic Radiosurgery Society assume no liability for the information, conclusions, and recommendations contained in this report.

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Supplemental digital content is *available for this article at www.neurosurgery-online.com.*

Supplemental Digital Content 1. Table. Search strategy.
Supplemental Digital Content 2. Table. Risk-of-bias assessment—Items.
Supplemental Digital Content 3. Table. Risk-of-bias assessment.