Stereotactic radiosurgery versus stereotactic radiotherapy in the management of intracranial meningiomas: a systematic review and meta-analysis

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OBJECTIVE Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) have been used as a primary treatment or adjuvant to resection in the management of intracranial meningiomas (ICMs). The aim of this analysis is to compare the safety and long-term efficacy of SRS and SRT in patients with primary or recurrent ICMs.

METHODS A systematic review of the literature comparing SRT and SRS in the same study was conducted using PubMed, the Cochrane Library, Google Scholar, and EMBASE from January 1980 to December 2018. Randomized controlled trials, case-control studies, and cohort studies (prospective and retrospective) analyzing SRS versus SRT for the treatment of ICMs in adult patients (age > 16 years) were included. Pooled and subgroup analyses were based on the fixed-effect model.

RESULTS A total of 1736 patients from 12 retrospective studies were included. The treatment modality used was: 1) SRS (n = 306), including Gamma Knife surgery (n = 36), linear accelerator (n = 261), and CyberKnife (n = 9); or 2) SRT (n = 1430), including hypofractionated SRT (hFSRT, n = 268) and full-fractionated SRT (FSRT, n = 1162). The median age of patients at the time of treatment was 59 years. The median follow-up duration after treatment was 35.5 months. The median tumor volumes at the time of treatment with SRS, hFSRT, and FSRT were 2.84 cm³, 5.45 cm³, and 12.75 cm³, respectively. The radiographic tumor control at last follow-up was significantly worse in patients who underwent SRS than SRT (odds ratio [OR] 0.47, 95% confidence interval [CI] 0.27–0.82, p = 0.007) with 7% less volume of tumor shrinkage (OR 0.93, 95% CI 0.61–1.40, p = 0.72). Compared to SRS, the radiographic tumor control was better achieved by FSRT (OR 0.46, 95% CI 0.26–0.80, p = 0.006) than by hFSRT (OR 0.81, 95% CI 0.21–3.17, p = 0.76). Moreover, SRS leads to a significantly higher risk of clinical neurological worsening during follow-up (OR 2.07, 95% CI 1.06–4.06, p = 0.03) and of immediate symptomatic edema (OR 4.58, 95% CI 1.67–12.56, p = 0.003) with respect to SRT. SRT could produce a better progression-free survival at 4–10 years compared to SRS, but this was not statistically significant (p = 0.29).

CONCLUSIONS SRS and SRT are both safe options in the management of ICMs. However, SRT carries a better radiographic tumor control rate and a lower incidence of posttreatment symptomatic worsening and symptomatic edema, with respect to SRS. However, further prospective studies are still needed to validate these results.

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KEYWORDS stereotactic radiosurgery; stereotactic radiotherapy; intracranial meningioma; Gamma Knife; CyberKnife; LINAC

INTRACRANIAL meningioma (ICM) constitutes 33.8% of all brain tumors and is almost always histologically benign (95%).⁴⁴ Atypical ICMs comprise 5%–15% and the malignant variety encompasses 1%–3% of meningiomas,³⁵ and is associated with a higher risk of tumor recur-

rence after surgery than benign meningioma.⁴⁴ Gross-total resection (GTR) using a microsurgical technique is the treatment of choice for easily accessible meningiomas.^{41,43} However, meningiomas adjacent to, or abutting, critical neural or vascular structures, such as skull base menin-

ABBREVIATIONS CI = confidence interval; EBRT = external beam radiation therapy; FSRT = full-fractionated SRT; GKS = Gamma Knife surgery; GTR = gross-total resection; hFSRT = hypofractionated SRT; ICM = intracranial meningioma; IMRT = intensity-modulated radiation therapy; LINAC = linear accelerator; OR = odds ratio; PFS = progression-free survival; RCT = randomized controlled trial; SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy; STR = subtotal resection.

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FIG. 1. Database search strategy of the included studies according to PRISMA criteria.

giomas, carry a significant risk of morbidity and mortality if GTR is pursued.²⁷ Stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS) have emerged as highly effective alternatives or as complements to resection. SRS and SRT have been used as primary therapy for benign meningioma, especially when located closer to critical areas, as well as for adjuvant treatment for residual or recurrent tumors.^{29,38} SRS carries a 5-year tumor control rate similar to GTR, with lower morbidity than surgery, especially for skull base lesions.¹ Moreover, adjuvant radiation treatment of meningiomas initially treated with subtotal resection (STR) results in a tumor control rate equivalent to GTR.³⁴ Radiation can be delivered using different techniques that are grouped into two categories, namely SRT and SRS. SRS includes one to a maximum of five sessions of Gamma Knife surgery (GKS),²⁸ linear accelerator (LINAC) treatment,^{22,42} and CyberKnife,²⁶ while SRT includes multisession hypofractionated SRT (hFSRT) and full-fractionated SRT (FSRT).^{8,18} However, there is no consensus on what is the best technique to treat ICMs.²⁵ We conducted a systematic review and meta-analysis including randomized-controlled trials (RCTs), case-control studies, and cohort studies (retrospective or prospective) comparing the clinical and radiological outcomes of adult patients with ICMs treated with SRS versus SRT.

Methods

The present review was performed according to the PRISMA guidelines for systematic reviews and meta-analyses.²¹

Eligibility Criteria

RCTs, case-control studies, and cohort studies (retrospective or prospective) investigating the clinical and radiological outcomes of SRS or SRT as primary or adjuvant treatment for ICM in the adult population (age > 16 years) were included. ICMs were defined as tumors derived from the arachnoid cap cells, and that are located within the skull. Optic nerve sheath meningiomas were excluded from this review because the use of radiation therapy remains controversial.³⁰ SRS was defined as radiation treatment delivered in 1 session to a maximum of 5 fractions. SRT was defined as radiation treatment delivered in more than 5 sessions^{14,15} and included hFSRT (5–10 fractions)^{8,14} and FSRT (> 10 fractions).^{14,18} No language or publication status restrictions were imposed.

Outcome Measures

Primary outcome measures included radiographic tumor control at last follow-up and clinical worsening at any stage of follow-up. Radiographic tumor control was defined as a stable appearance or shrinkage of the tumor noted on CT or MRI. Clinical worsening was defined as a decline in neurological symptoms.

Secondary outcome measures included tumor shrinkage at last follow-up, symptomatic edema immediately after radiation treatment, and progression-free survival (PFS). Tumor shrinkage was defined as regression in tumor volume. PFS was defined as length of time after radiation treatment to disease progression or death from any cause.

TABLE 1. Baseline characteristics of the included patients

Authors & Year	No. of Pts (tumors)	Median Age (range), yrs	Meningioma		Op: Primary RT	Median Tumor Vol (cm ³)	Radiation		Median FU SRS/ SRT (mos)	Indication for Tx
			Location (n)	Histological Grade			Tx Modality (n)	Dose in cGy & Fractions		
Lo et al., 2002	53 (63)	66 (22–85)	Petroclival (10), sphenoid (19), & cavernous sinus; optic nerve sheath (1), convexity (19), cerebellar (4), parasagittal (4), tentorial (6)	Grade 1, 47 (74.6%); grade 2, 5 (7.9%); grade 3, 11 (17.4%)	Prior op, 5/53 (9.4%); primary, 48/53 (90.6%)	6.8/8.8	SRS (35), FSRT (18, LINAC-based)	SRS, 1400 (500–4500); FSRT, 5400 (4000–6000), 30 fractions (16–31)	38/30.5	Pts w/ meningiomas < 5 mm from critical structures such as the optic chiasm & brainstem or tumors of large size (usually 4 cm or larger) were selected for FSRT
Torres et al., 2003	128 (156)	57.2 (18–87)	ICM, 156	NA	Prior op, 84/161 (52.1%); primary, 44/161 (27.3%)	12.7/16.1	SRS (79), FSRT (77, LINAC-based)	SRS, 1567; FSRT, 4839	40/24	SRS is indicated for ICMs < 3 cm or 20 ml in vol & w/ min distance from the optic apparatus of 2–4 cm
Metellus et al., 2005	74	51.2 (53)	Cavernous sinus meningioma	Grade 1, 14 (18.9%); GKS; 23 (31%); FSRT	GKS: prior op, 13; primary, 23; FSRT: prior op; 17; primary, 15	5.2/13.5	GKS (36), FSRT (conventional EBRT), 38	GKS, 1500; FSRT, 5300	63.6/88.6	Pts w/ tumors > 3 cm, showing a close relationship w/ optic apparatus (3 mm) or skull base dural spreading, were treated by FSRT
Henzel et al., 2006	224	59 (22–85)	Frontobasal (3), optic nerve (6), cavernous sinus (134), petroclival (37), tentorial (17), falxial (19), others (8)	Grade 1, 113 (50.4%); grade 2, 10 (4.5%); grade 3, 6 (2.6%)	Prior op, 129/224 (57.6%); SRT/ SRS, 95/224 (42.4%)	1.9/3.8/12.0 (SRS/hFSRT/ SRT)	SRS (11), hFSRT (30), SRT (183, LINAC-based)	SRS, 1500–1800, 1 fraction; hFSRT, 400, 10 fractions, or 500, 5–7 fractions; SRT, 5580	36	SRT: tumors > 4 ml, distance to critical structures < 2 mm; hSRT: > 4 ml, distance > 2 mm; SRS: < 4 ml, distance > 2 mm
Girvigian et al., 2008	32	59 (22–84); 57 (29–75)	Convexity (18), parasagittal (20)	Grade 2, 4 (12.5%)	Prior op, 16/32 (50%); primary, 14/32 (44%)	2.84/7.46	SRS (14), FSRT (16, LINAC-based)	SRS, 1400; FSRT, 5040, 28 fractions	20/18	Pts w/ incomplete resection (grade III or IV) for convexity or parasagittal meningiomas are candidates for conformal EBRT or SRS; GKS Tx was used for tumors < 3 cm in size, at least 3 mm distant from the optic nerve, & the absence of dural spreading on the cranial base
Hamm et al., 2008	224	59 (22–85)	Skull base meningioma	Grade 1, 196 (87.5%); grade 2, 17 (7.5%); grade 3, 10 (4.5%)	Prior op, 129/224 (57.6%); primary, 95/224 (42.4%)	0.16–3.56/135	SRS (11), hFSRT (30), FSRT (183, LINAC-based)	SRS, 1280–1800; hFSRT, 400, 10 fractions, or 500, 6–7 fractions; SRT, 5580	36	SRT consisted of the tumor vol + a safety margin of approx. 2 mm for WHO grade I & II meningiomas & 5 mm for WHO grade III meningiomas

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TABLE 1. Baseline characteristics of the included patients

Authors & Year	No. of Pts (tumors)	Median Age (range), yrs	Meningioma		Op: Primary RT	Median Tumor Vol		Radiation		Median FU SRS/ SRT (mos)	Indication for Tx
			Location (n)	Histological Grade		SRS/SRT (cm ³)	Tx Modality (n)	Dose in cGy & Fractions			
Eldebawy et al., 2011	32	44 (21–67)	Sellar & parasellar (10), lobar (9), cavernous sinus (5), skull base (8)	Grade 1, 32 (100%)	Prior op, 18/32 (56.2%); primary, 14/32 (43.7%)	9.2 (1.8–39.7)	SRS (19), hFSRT (13)	NA	39	SRS: radiological well-defined lesion, small vol & away from critical structures; hFSRT: large vol lesions involving critical structures	
Han et al., 2014	213 (220)	59 (28–84)	Basal meningiomas	SRS/SRT: grade 1, 12 (5.5%)/42 (19%); grade 2, 3 (1.3%)/4 (1.8%); grade 3, 3 (1.3%)/7 (3.1%); Unknown: 3 (1.3%)/7 (3.1%)	Prior op, 74 (33.6%), 25 GTR, 44 STR, 5 biopsy; primary, 146 (66.3%)	2.8/4.8/11.1	X-Knife SRS (55), hF-SRT (22), FSRT (143), LINAC-based)	SRS, 1250, 1 fraction; hFSRT, 2500, 5 fractions; FRT, 5040, 28 fractions	32	SRS: tumors located in the CPA < 3 cm in max diameter, in anterior skull base tumor < 3 cm in diameter & at least > 2 mm from the optic apparatus; FRT: pts w/ tumor causing optic nerve/chiasm dysfunction, or < 2 mm from the optic structures or large tumor diameter (> 3 cm); hFSRT: tumor size btwn 3 & 5 cm in diameter & > 2 mm from the optic apparatus	
Kaul et al., 2014	297	59	Skull base (254), falx (20), convexity (23)	Grade 1, 50 (16.8%); grade 2, 20 (6.7%); grade 3, 12 (4.04%); no histology = 215 (72.4%)	Prior op, 158/297 (53.2%); primary, 144/297 (48.5%)	15.01	SRS (26), hFSRT (92), FSRT (179), LINAC-based)	SRS, 1730; hFSRT, 3760; FSRT, 5731	35	Tumors in close proximity to critical structures were assigned to FSRT, while large tumors (> 2 cm) distant to critical structures underwent hFSRT & small tumors (< 2 cm) were treated by SRS	
Fokas et al., 2014	318	66 (13–85)	Olfactory (3), optic (14), sphenoid wing (100), cavernous sinus (69), petroclival (39), temporal (13), falx (27), tentorium (8), frontobasal(15), occipital (4), CPA (8), overlapping(18)	Grade 1, 318 (100%)	NA	1.84/6.11/16.0	SRS (16), hFSRT (49), FSRT (253), LINAC-based)	hFSRT, 400, 10 fractions, or 500, 5–7 fractions; FSRT, 5580	50	FSRT: tumor size > 4 cm ³ , distance to critical structures < 2 mm, 49 pts (15.4%); hFSRT: tumor size > 4 cm ³ , distance > 2 mm to critical structures, & 16 pts (5.0%) were treated w/ SRS (tumor size < 4 cm ³ , distance > 2 mm)	

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TABLE 1. Baseline characteristics of the included patients

Authors & Year	No. of Pts (tumors)	Median Age (range), yrs	Meningioma		Op: Primary RT	Median Tumor Vol		Radiation		Median FU SRS/ SRT (mos)	Indication for Tx
			Location (n)	Histological Grade		SRS/SRT (cm ³)	Tx Modality (n)	Dose in cGy & Fractions			
Knitter et al., 2015	100	60 (23–89)	Skull base (32), cavernous sinus (21), CPA (13), convexity (13), dural sinus (8), posterior fossa (7), orbit (5), other (5)	Grade 1, 25; grade 2, 10; grade 3, 2	NA	NA	SRS (11), hSRT (18, LINAC-based), IMRT (72)	SRS, 1500, 1 fraction; hSRT, 2500, 5 fractions; IMRT, 5220, 30 fractions	12		
Manabe et al., 2017	41	70 (33–92)	Convexity (11), falx (8), parasagittal (4), tentorial (3), petroclival (2), lat ventricle (1), tuberculum sellae (1)	NA	NA	9/32	SRS (9), hF-SRT (32), CyberKnife based	SRS, 1700; hF-SRT, 2500	49	SRS & hSRT were used for small tumors (< 13.5 ml, 30 mm in diameter)	

Approx. = approximately; CPA = cerebellopontine angle; FU = follow-up; NA = not available; pt/pts = patients; RT = radiotherapy; SRT = subtotal resection; Tx = treatment.

Information Sources

The following databases were reviewed: PubMed, Cochrane Library, Google Scholar, and EMBASE. In addition, we reviewed the unpublished “gray” literature including unpublished abstracts from European and American Radiation Oncology conferences over the last 30 years related to SRS and SRT for ICM. However, none of the abstracts met our inclusion criteria. Articles published between January 1980 and December 2018 were searched. The last search was performed on December 11, 2018 (Fig. 1).

Literature Search

The following MeSH headings were searched: “radio-surgery”, “radiotherapy”, and “meningioma”. A total of 150 articles were retrieved using these MeSH headings.

Study Selection and Data Extraction

Eligibility assessment was performed independently in an unblinded standardized manner by 2 reviewers (N.F. and A.M.), on the basis of the inclusion criteria. Disagreements between the reviewers were resolved by consensus. We developed the data extraction sheet based on the Cochrane Consumers and Communication Group’s data extraction template. No author was contacted for further information and data were extracted from the articles.

Data Items

Information was extracted from each study, including: 1) demographic characteristics of patients (median age at time of treatment, median tumor size, tumor location, prior resection, and histological grade of tumor); 2) radiation treatment characteristics (radiation technique, median radiation dose, and median number of fractions); and 3) outcome measures (radiographic tumor control, tumor shrinkage, clinical worsening during follow-up, and PFS).

Risk of Bias in Individual Studies

Before conducting studies, we hypothesized that the effect size was the same.

Summary Measures

The meta-analysis was performed by computing odds ratios (ORs) using a fixed-effects model. Quantitative analysis was performed on the radiographic tumor control at last follow-up and clinical response. ORs and 95% confidence intervals (CIs) for each clinical outcome were calculated.

Planned Method of Analysis

The Review Manager program (version 5) as provided by the Cochrane Library was used to perform statistical analysis. The data from each study was extracted from the articles processed by the software to perform a pooled meta-analysis and subgroup analysis. The radiographic tumor control provided by SRS was computed against SRT and further subgroup analysis was performed by comparing SRS against the hFSRT and the FSRT. Further analysis included tumor shrinkage, clinical worsening,

TABLE 2. Clinical & radiological outcomes in the included studies

Authors & Year	SRS vs SRT				
	Radiographic Tumor Control at Last Follow-Up	Tumor Size at Last Follow-Up	Clinical Outcome at Follow-Up	Postop Immediate Symptomatic Edema	PFS at 4–10 yrs
Lo et al., 2002	12/35 (34.3%) vs 5/18 (28%)	Shrinkage, 4/35 (11.4%) vs 1/18 (5.6%); stabilized, 8/35 (23%) vs 4/18 (22.2%)	NA	NA	NA
Torres et al., 2003	58/79 (73.4%) vs 70/77 (91%)	Shrinkage, 22/79 (28%) vs 24/77 (31.1%); stabilized, 36/79 (46%) vs 46/77 (60%)	Improved, 22/79 (28%) vs 21/77 (27.2%); worsened, 5/79 (6.3%) vs 2/77 (3%)	NA	NA
Metellus et al., 2005	34/36 (94.4%) vs 38/38 (100%)	Shrinkage, 19/36 (53%) vs 11/38 (29%); stabilized, 15/36 (42%) vs 27/38 (71%)	Improved, 21/36 (58.3%) vs 24/38 (63.2%); worsened, 2/36 (5.6%) vs 1/38 (2.6%)	NA	34/36 (94.4%) vs 37/38 (97.4%) at 10 yrs
Henzel et al., 2006	124/219 (56.6%, combined SRS/SRT outcome)	Shrinkage 100/219 (46%)	Improved, 95/219 (43.3%); worsened, 1/11 (9.1%) vs 21/213 (10%)	NA	96.9%
Girvigian et al., 2008	NA	NA	Worsened, 6/14 (43%) vs 1/16 (6.25%)	6/14 (42.3%) vs 1/16 (6.25%)	NA
Hamm et al., 2008	NA	NA	Improved, 31/32 (97%); worsened, 1/32 (3.1%)	NA	217/224 (97%)
Eldebawy et al., 2011	30/32 (94%)	Shrinkage, 10/32 (31.2%); stabilized, 20/32 (62.5%)	Improved, 22/32 (69%); worsened, 10/32 (31.2%)	NA	94%
Han et al., 2014	SRS/hFSRT/FSRT: 50/55 (91%) vs 21/22 (96%) vs 36/143 (95%)	Shrinkage, 12/55 (22%) vs 9/22 (41%) vs 49/143 (34%); stabilized, 38/55 (69%) vs 13/22 (59%) vs 90/143 (63%)	Improved, 13/55 (23.6%) vs 4/22 (18.1%) vs 46/143 (32.2%); worsened, 6/55 (11%) vs 0/22 (0%) vs 13/143 (9.1%)	6/55 (11%) vs 0/22 (0%) vs 6/143 (4.2%)	48/55 (87.2%) vs 20/22 (91%) vs 131/143 (92%) at 4 yrs
Kaul et al., 2014	NA	NA	NA	NA	23/26 (88.5%) vs 74/92 (80.4%) vs 155/179 (87%) at 10 yrs
Fokas et al., 2014	295/318 (92.7%)	NA	NA	NA	NA
Knitter et al., 2015	9/11 (81.8%) vs 14/18 (77.8%) vs 66/72 (91.7%)	NA	NA	NA	9/11 (81.8%) vs 14/18 (77.8%) vs 66/72 (91.7%) at 5 yrs
Manabe et al., 2017	NA	Shrinkage, 12/41 (29.2%); larger, 5/41 (12.2%)	NA	NA	8/9 (89%) vs 32/32 (100%) at 5 yrs

and symptomatic edema and PFS. The OR from separate studies was then analyzed against the fixed-model effect. Heterogeneity between studies was assessed with the I^2 statistic.

Risk of Bias Across Studies

None of the included studies was an RCT. Double-blindedness was not achieved in any of the studies. However, high heterogeneity with significant p values was observed in studies involving tumor shrinkage. This was further analyzed using funnel plots that showed asymmetrical distribution. Removal of 1 study decreased the heterogeneity, which indicated that the bias could be due to sample size.

Results

Study Selection

Figure 1 shows a flow diagram of study selection accord-

ing to PRISMA guidelines.²¹ A total of 1100 articles were retrieved from PubMed, the Cochrane Library, Google Scholar, and EMBASE. Of 150 eligible articles, 84 were excluded due to missing quantitative outcome data and 54 studies did not present the long-term follow-up, beyond 1 year. No other unpublished studies or abstracts were included. Hence, 12 studies were included in the meta-analysis.

Study Characteristics

All included studies were retrospective. The studies were performed in the US ($n = 6$), Germany ($n = 3$), France ($n = 1$), Japan ($n = 1$), and Egypt ($n = 1$). The studies reported the treatment of patients with SRS ($n = 306$), including GKS ($n = 36$), LINAC ($n = 261$), and CyberKnife ($n = 9$), or SRT ($n = 1430$), including hFSRT ($n = 268$), FSRT ($n = 1090$), and IMRT ($n = 72$). The baseline characteristics and outcomes of the included patients are reported in Tables 1–3.

TABLE 3. Demographics of the included patients

Characteristic	All (n = 1736)	SRS (n = 306)	hFSRT (n = 268)	FSRT (n = 1162)
Median age (yrs)	59	59	59	59
Location skull base				
Not specified	738			
Cavernous sinus	424			
Sphenoid wing	119			
Petroclival	88			
Tentorial	34			
Olfactory	21			
Frontobasal	18			
Parasellar/sellar	10			
CPA	8			
Tuberculum sellae	1			
Supratentorial				
Convexity	84			
Parasagittal	28			
Falx	74			
Infratentorial	15			
Others	187			
Tumor histological grade				
1	828			
2	70			
3	48			
No histology	222			
Prior microsurgery	643			
Median tumor vol at time of treatment, cm ³	5.45	2.84	5.45	12.75
Median margin dose, cGy	3375	1520	3375	5350
Median no. of fractions	5–10	<5	5–10	>10
Median follow-up, mos	35.5	37	36	33.5

Values presented as number of patients unless indicated otherwise.

The median age of patients at the time of treatment was 59 years. Six hundred forty-three patients (37%) underwent prior microsurgical resection. Eight hundred sixty tumors were benign meningiomas (73.6%), 70 were atypical meningiomas (6%), and 48 were malignant meningiomas (4%). The median tumor sizes at the time of treatment with SRS, hFSRT, and FSRT were 2.84 cm³, 5.45 cm³, and 12.75 cm³, respectively. The median margin doses and fractions for SRS, hFSRT, and FSRT were 1520 cGy in 1 fraction, 3375 cGy in 5–10 fractions, and 5350 cGy in more than 10 fractions (28–30), respectively. The median follow-up duration was 35.5 months.

Study Outcomes

Overall, radiographic tumor control at last follow-up was achieved in 75.5% and 90.2% of patients who received SRS and SRT, respectively. In a pooled meta-analysis of included studies, SRS was significantly associated with a lower likelihood of radiographic tumor control at last follow-up than SRT (OR 0.47, 95% CI 0.27–0.82, $p = 0.007$; Fig. 2A). Further analysis indicated that, with respect to

SRS, tumor control was better achieved by FSRT (OR 0.46, 95% CI 0.26–0.80, $p = 0.006$) than by hFSRT (OR 0.81, 95% CI 0.21–3.17, $p = 0.76$; Fig. 2B and C).

Tumor shrinkage at last follow-up occurred in 31.5% of meningiomas treated with SRT, whereas this occurred in 27.8% of meningiomas treated with SRS. Moreover, SRS carried a 7% less extent of tumor volume shrinkage at last follow-up with respect to SRT (OR 0.93, 95% CI 0.61–1.40, $p = 0.72$; Fig. 3).

During clinical follow-up, 10.2% and 6% of patients who received SRS and SRT, respectively, experienced clinical worsening. In addition, the incidence of symptomatic edema was found to be higher in patients treated with SRS (17.4%) than with SRT (4%). In a subgroup analysis, SRS had a 2-fold higher likelihood of clinical worsening during follow-up (OR 2.07, 95% CI 1.06–4.06, $p = 0.03$) and 4 times higher risk of immediate postradiation symptomatic edema (OR 4.58, 95% CI 1.67–12.56, $p = 0.003$; Fig. 4) with respect to SRT.

PFS at 4–10 years was achieved in 89% and 88.8% in the cohort of patients treated with SRS and SRT, respectively. Furthermore, SRT could lead to a better, yet statis-

FIG. 2. Radiographic tumor control at last follow-up. Pooled meta-analysis of all included studies. **A:** SRS compared to SRT (hFSRT/FSRT). SRS provides a worse radiographic tumor control at last follow-up than SRT (OR 0.47, 95% CI 0.27–0.82, $p = 0.007$). **B:** SRS compared to FSRT. FSRT provides better tumor control than SRS (OR 0.46, 95% CI 0.26–0.80, $p = 0.006$). **C:** SRS compared to hFSRT. hFSRT could provide better tumor control than SRS, but the difference is not statistically significant (OR 0.81, 95% CI 0.21–3.17, $p = 0.76$).

tically nonsignificant, PFS at 4–10 years than SRS (OR 0.72, 95% CI 0.38–1.34, $p = 0.29$; Fig. 5).

Discussion

In this study we present a systematic review and meta-analysis of the outcomes of patients affected with ICM who underwent SRS or SRT, with or without prior resection. The vast majority of patients (1162, 67%), were treated by FSRT. In all studies together, a total of 643 tumors (37%) underwent prior resection, while the remaining 63% of tumors received either SRS or SRT as primary treatment. SRT was used to treat larger tumor volumes (median 12.75 cm³ for FSRT, 5.45 cm³ for hFSRT) with respect to SRS (median tumor volume 2.84 cm³). These findings are consistent with those in previously published literature²⁰

and with the European Association of Neuro-Oncology (EANO) guidelines recommending treatment of smaller meningiomas with SRS, and treatment of larger or recurrent meningiomas with SRT.^{5,11,16,33} SRT and other external beam radiation therapy (EBRT) techniques (such as conventional 3D or intensity-modulated radiation therapy [IMRT]) are distinguished by the accuracy of the treatment delivery, based on intrafraction and interfraction accuracy.^{9,37} SRT is fractionated treatment delivered with the same principles guiding (single-fraction) SRS.³⁷ Therefore, as defined by society-accepted practice guidelines,³⁷ SRS is defined as “radiation therapy delivered via stereotactic guidance with approximately 1 mm targeting accuracy to intracranial targets in 1 to 5 fractions.” Conversely, SRT is treatment with the same level of accuracy, but with more than 5 fractions.³⁷

FIG. 3. Subgroup analysis of tumor shrinkage in SRS versus SRT (hFSRT/FSRT) at last follow-up. The comparison demonstrated 7% less volume of tumor shrinkage with SRS than SRT (OR 0.93, 95% CI 0.61–1.40, $p = 0.72$).

FIG. 4. Clinical outcomes during follow-up. The *upper panel* shows worsening of clinical outcome during follow-up in patients treated with SRS versus SRT. SRS carried a significantly higher risk in the rate of symptomatic worsening during follow-up (OR 2.07, 95% CI 1.06–4.06, $p = 0.03$). The *lower panel* compared the immediate symptomatic edema of SRS and SRT (OR 4.58, 95% CI, 1.67–12.56, $p = 0.003$).

In our study we found that SRT is significantly associated with better radiographic tumor control and with higher extent of tumor shrinkage at last follow-up compared to SRS ($p = 0.007$ and $p = 0.72$, respectively). These findings are consistent with a previous meta-analysis of skull base meningiomas²⁹ that reported a local tumor control rate at 5 years with SRT of 85%–100%, while with SRS the rate was 85%–97%. However another retrospective series investigating cavernous sinus meningiomas²⁰ found that monofractionated treatment (GKS and LINAC) induced more tumor shrinkage than FSRT (52.5% vs 20%, $p = 0.001$). In the same study, the mean radiated tumor volume was 7.4 cm³ and 6.8 cm³ for GKS and LINAC, respectively, whereas for SRT the volume was 12.6 cm³. A potential explanation for the contradictory findings of our study with respect to the study by Leroy et al. is that in our review the mean tumor volume of meningiomas treated with SRS was 2.84 cm³, while the tumor volume of meningiomas treated with SRT was larger (median 12.75 cm³ for FSRT and 5.45 cm³ for hFSRT). The difference in radiographic tumor control could be explained by a systematic error in the measurement of the tumor size change in the case of small meningiomas, which were usually treated with SRS instead of SRT. However, improved radiograph-

ic tumor control and a lower incidence of adverse effects (clinical worsening and symptomatic edema) provided by SRT with respect to SRS could be also explained by the biological effects of dose fractionation. In fact, fractionation allows SRT to deliver a higher radiation dose, even to complex-shaped tumors, with high precision and accuracy, and minimize the unwanted dose to the adjacent healthy tissues.²⁴ This hypothesis is strengthened by the fact that, with respect to SRS, tumor control was better achieved by FSRT (OR 0.46, 95% CI 0.26–0.80, $p = 0.006$) than by hFSRT (OR 0.81, 95% CI 0.21–3.17, $p = 0.76$).

The clinical outcomes varied significantly across studies reporting the use of SRS and SRT ($p = 0.03$). Overall, patients treated with SRS experienced clinical worsening during follow-up twice as frequently as those treated with SRT. However, some studies failed to reveal any statistically significant difference in the risk of clinical worsening between SRS and SRT.²⁰ From a radiobiological perspective, SRS is delivered in very few fractions, carrying a higher risk of direct vascular injury and release of various tumor-specific antigens and inflammatory cytokines. These effects, along with tumor progression, could result in clinical and neurological worsening.⁴⁰ Accordingly, postradiation symptomatic edema was significantly more

FIG. 5. PFS at 4–10 years of patients treated with SRT could be longer than SRS, although the difference was not statistically significant (OR 0.72, 95% CI 0.38–1.34, $p = 0.29$).

frequently associated with SRS than with SRT ($p = 0.003$). Specifically, SRS can induce disruption of the tumor-brain interface, leading to spread of vasogenic fluid into the brain tissue and causing formation/aggravation of peritumoral edema.^{2,39}

PFS at 4–10 years was better achieved in a cohort of patients who received SRT compared to SRS, although the difference between the two techniques was not statistically significant ($p = 0.29$). These findings are consistent with previous studies showing that the 5-year PFS for meningiomas treated with SRS was 94%–98.5%,^{4,19,31} with LINAC 95%–96%,^{32,43} with FSRT 97.4%, and with hFSRT 96.9%.^{3,36}

The present meta-analysis includes a large population of patients. However, there are several limitations to this study. First, the included studies presented relatively small retrospective series, lacking randomization and control groups. Second, different studies adopted different treatment protocols including, but not limited to, radiation dose, fractionation, radiation technique, and indications for treatment. Different patients within a single study cohort were sometimes treated with different radiation techniques.^{8,13,14,17,18} In these studies, the results of different radiation techniques could be affected by a selection bias. Third, the evolution of the histological classification and grading of meningiomas might have affected our results. In fact, the series included in the present review was published over more than one decade, between 2002 and 2017. In the same temporal span, the classification of meningioma changed^{12,23} and, as a consequence, the same tumor could have been included under different categories in different studies. Moreover, a few studies did not report the histological grade of the meningiomas at all. Fourth, the RECIST (Response Evaluation Criteria in Solid Tumors) criteria⁶ for assessing tumor response to the treatment were not consistently followed. Specifically, although the studies used MRI with contrast enhancement for radiological follow-up, the definition of tumor progression or response was not always described, or varied across different studies. Therefore, further studies are required to validate our findings and should include randomized controlled trials comparing the treatment strategies of ICMs.

Conclusions

SRS and SRT are highly effective treatment modalities in the management of ICM either as primary or adjuvant therapy. FSRT and hFSRT achieved better radiographic tumor control and greater extent of tumor shrinkage in comparison to SRS. SRS has a higher risk of clinical deficits and symptomatic edema risk in comparison with SRT. However, PFS is not significantly different across the two techniques. Further prospective studies are needed to investigate and compare the risks and benefits of SRT and of SRS for ICMs.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Fatima. Analysis and interpretation of data: Fatima, Meola. Critically revising the article: Meola, Pollom, Soltys. Statistical analysis: Fatima. Study supervision: Chang.

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