

Stereotactic radiosurgery: a meta-analysis of current therapeutic applications in neuro-oncologic disease

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Abstract Stereotactic radiosurgery (SRS) represents an important tool in neurosurgery and radiotherapy for addressing a multitude of diseases, most notably in the field of neuro-oncology. The pathologies for which it is employed vary significantly, and few controlled studies exist to evaluate its efficacy. We aimed to provide a quantitative meta-analysis of SRS applications in neuro-oncology, providing benchmarks for expected outcomes. The meta-analysis was conducted in accordance with established standards for evaluating observational data. Specific inclusion criteria were utilized, search terms recorded, and data extracted to summarize demographic and outcome statistics. Meta-analysis was conducted where statistically appropriate, and clinical outcomes summarized as tumor stability, survival, and complications in a pathology-specific manner. For vestibular schwannoma, 37 studies with a total 3,677 patients were included. Overall disease stabilization rate after adjustment for significant publication bias was 91.1%. Non-cranial nerve complication rate after publication bias adjustment was 5.6%. Accounting for publication bias, rate of hearing preservation was with 59.3%. For 456 glioblastoma multiforme (GBM) patients in 11 studies receiving SRS, median survival from diagnosis was 13.5–26 months, while overall complication rate was 11.4%. For meningioma, 15 studies with a total 2,734 patients were included; 77.1% were classified as skull base. Overall disease stabilization rate was 89.0, while overall complication rate was 7.0%. For metastatic disease, 27

studies with a total of 2,679 patients were included. Overall median survival from time of SRS was 5–14 months, overall 1-year survival rates were 15–54.9%, while reported local disease control rates were 59.6–96.8%. Stereotactic radiosurgery is an increasingly important tool in the management of neuro-oncologic diseases. While there is a pathology-specific role for SRS, current data show excellent results in treating several pathologies. As such, SRS adds significantly to the neurosurgical armamentarium for treating neuro-oncologic processes.

Keywords Stereotactic radiosurgery · Neuro-oncology · Vestibular schwannoma · Glioblastoma multiforme · Metastatic disease · Meningioma

Leksell first described delivery of concentrated radiation to intracranial targets over five decades ago [1]. This ‘radiosurgery’ utilizes image guidance to aim multiple highly-focused beams of radiation at a target from multiple directions along in three dimensions. The introduction of the cobalt-60 gamma unit in 1968 represented a concrete application of the radiosurgery concept [2], and the gamma knife and linear accelerator represent modern tools of this technology. Proton-beam therapy, while utilizing a different form of radiation, also represents a similarly highly focused and targeted radiation tool. Recent advances in imaging techniques, combined with high-powered computer information systems with high-speed algorithms and 3-D rendering have allowed integration of data, and have facilitated improved targeting of intracranial pathology while sparing surrounding neurovascular structures. With such advances, stereotactic radiosurgery (SRS) represents an attractive minimally invasive tool for addressing intracranial pathology.

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A number of radiation-based modalities are currently available for treating intracranial tumors. External beam radiation therapy (EBRT) uses uniform doses of radiation delivered to large tissue volumes often in multiple sessions. Examples include whole-brain radiation therapy (WBRT) and conformal radiation therapy. SRS delivers focused radiation to a specific target using precise neuronavigation with minimal effect on surrounding structures in a single session [3, 4]. Fractionated and hypofractionated stereotactic radiotherapy utilize the same neuronavigational targeting principles, but spread treatment over multiple sessions with smaller per-session dose. Thus, the emphasis of SRS is maximizing dose while limiting volume of distribution to the target lesion. Though many publications have studied each of these modalities, examining SRS alone provides a focused review of advances in targeted radiation applied to neuro-oncology.

As SRS technology has advanced, its applications to neuro-oncology have expanded to include vestibular schwannomas, skull base meningiomas, intracranial metastases, and high-grade gliomas [5–8]. To gain a thorough understanding of the current status of SRS, we aim to provide an evidence-based, quantitative pathology-based review on these most thoroughly studied oncologic applications. This analysis aims to provide clinical outcome benchmarks for major intracranial SRS applications that can aid the general practitioner in understanding its promise and limitations.

Methods

Search strategy

The study was designed to meet standards for observational meta-analysis [9]. Search databases included Pubmed and Ovid, and were executed for each pathology using specific keywords. Keywords included “SRS,” “stereotactic radiosurgery,” “Gamma Knife,” and “Linear Accelerator,” and pathology-specific terms: “acoustic neuroma,” “vestibular schwannoma,” “glioblastoma multiforme,” “high-grade glioma,” “metastases,” and “meningioma.” Individual publications up to November, 2008 were screened using specific inclusion criteria. Hand-searching was conducted using references from papers acquired using the computer searches.

Inclusion/exclusion criteria

Demographic information was recorded, and studies lacking one or two demographic variables were included if they met outcome variable criteria. Studies reporting fractionated radiotherapy treatment regimens were excluded as the variance in fractionation would introduce excessive

variability into the analysis. Only studies reporting pathology-appropriate outcomes were included. For studies of glioblastoma multiforme (GBM), only patients with GBM were included. These included survival for malignant tumors, and tumor control rates. Case reports and articles in languages other than English were excluded. In order to avoid repeat patient data, each group or institution was limited to one included study unless different publications from one institution clearly reported unique patient series. For studies where outcome data were lacking, efforts were made to contact authors to obtain the data. Studies focusing on a population subgroup (i.e. presenting outcomes only from patients with neurofibromatosis II) were excluded. Studies were screened independently by two nonblinded authors. As the aim was to provide a set of outcome benchmarks, a study was included for analysis as long as both screeners agreed that it met inclusion criteria. Studies that were ruled out were recorded, along with the reasons for the exclusion.

Statistical analysis

Outcome variables from included studies underwent meta-analysis to yield overall rates and 95% confidence intervals (95%CI) where applicable. Calculations were made using the random-effects model; if there was no significant heterogeneity, the fixed-effects model was used. Publication bias arises from the tendency for only positive results to be published; as a result, conclusions from a meta-analysis may be skewed since they are based only on an analysis of data from publications. The presence of publication bias was examined using the regression-based Egger’s test, and adjustments were performed using Duval and Tweedie’s Trim and Fill algorithm [10, 11].

Results

Vestibular schwannoma

Of 83 studies found, 37 studies met inclusion criteria [8, 12–47], while 46 were excluded [48–93]. The most common reason for exclusion was publication from a group with an already included study (24 studies) [48–50, 53, 56, 57, 59–62, 64–68, 70, 74, 77–79, 86, 90, 91, 93]. Included studies were case series, representing class III evidence. Figure 1a summarizes demographic and treatment data. About 3,677 patients were included; study sample sizes ranged from 26 to 390. Age ranged from 10 to 92 years; cited mean/median ages ranged from 41 to 68 years. Tumor volumes varied widely, ranging 0.008–37.5 cm³; mean/median range was 1.3–7.6 cm³. Many patients had undergone previous surgical resection; the rate varied from

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Study ID	Group	Age			Tumor Volume (cm ³)			Follow-up (months)		% Post-Resection	Modality	Maximal Dose (Gy)		Margin Dose (Gy)	
		Total N	Mean (Median)	Range	Female - N(%)	Mean (Median)	Range	Mean (Median)	Range			Mean (Median)	Range	Mean (Median)	Range
Noren AN 1993	Karolinska Hospital, Sweden	254						54	12-206		GKS	15-25		10-20	
Foote IJROBP 1995	Mayo Clinic, MN	36	(68)	25-92	17 (47.2)	(3.1)	0.3-8.7	(16)	2.5-36	22.2	GKS	(36)	25-40	(20)	16-20
Hirato SFN 1996	Maebashi, Japan	29	47.7	24-71	17 (58.6)			27.6	24-40		GKS	(25.2)	17-34	12.1	9.9-17
Kondziolka NEJM 1998	U. Pittsburgh	162	60	28-83	91 (56.2)					25.9	GKS	32.7	24-50	16.6	12-20
Kwon SFN 1998	U. Ulsan, Seoul, S. Korea	88	43.7	13-72				52	7-84	40.9	GKS			12.6	
Vermuelen SFN 1998	U. Washington, Seattle	52	58.3		26 (50.0)	3.3	0.4-4.0	18.6	1.2-39.6		GKS			15.3	10-18
Unger AN 1999	Graz, Austria	56	(54)	16-79	27 (48.2)			(62)	48-80	0.0	GKS				12-14
Prasad JNS 2000	UVA, Charlottesville	153	65.1	19.8-90.4	73 (47.7)	2.7	0.02-18.3	51.2	12-120	37.3	GKS	34.3	17-53	13.2	9-20
Suh IJC 2000	Cleveland Clinic, Cleveland	29	(67)	26-83	18 (62.1)	(2.1)	0.2-28.7	(49)	4-110		LINAC			(16)	8-24
Andrews IJROBP 2001	Thomas Jefferson U., Philadelphia	69	61		36 (52.2)			29.8		24.6	GKS			50	
Bertalanffy AN 2001	Vienna, Austria	41	65	34-84	7 (17.1)					51.2	GKS			(12)	10-17
Lee SFN 2001	Adelaide, Australia	42						(25)		7.1	LINAC		13.3-19.9	(12)	12-14
Petit NSGY 2001	U. Maryland, Baltimore	47	(59)	19-83	20 (42.6)			(42)	12-84	25.5	GKS	(24)	12-35	(12)	7.5-15
Spiegelmann JNS 2001	Tel Hashomer, Israel	44	57	29-78	26 (59.1)	3.8	1-11	32	12-60	22.7	LINAC			14.6	11-20
Karpinos IJROBP 2002	Baylor, Houston	73	61.6 (62.5)	34-84	50 (68.5)			46.7 (48)	3-84	13.7	GKS	28.6	20-48	14.5	10-24
Ottaviani AOHNS 2002	Milan, Italy	30	54.6		17 (56.7)	1.6	0.2-4.9	24 (24)			GKS	25	17.5-28	13.4	12-14
Delbrouck AOLB 2003	Brussels, Belgium	95	(54.8)	10-89	37 (38.9)	1.4	0.01-7.5	(12)		14.7	GKS	(24.4)	22-28	(12.3)	12-14
Iwai NSGY 2003	Osaka, Japan	51	55	32-76	32 (62.7)	(3.6)	0.7-24.9	(60)	18-96	17.6	GKS			(12)	8-12
Litvack NF 2003	Brown U., Providence	134	55.3	13-86	70 (52.2)			31.7	12-72	13.4	GKS	25.4	17.4-34.3	12 (12)	
Meijer IJROBP 2003	Amsterdam, The Netherlands	49	63		25 (51.0)			30	12-107		LINAC			(12.5)	10-12.5
Rowe JNNP 2003	Sheffield, UK	232	56	23-85	129 (55.6)			35 (34)		25.4	GKS			14.6 (15)	
Chung IJROBP 2004	Vancouver, Canada	45	(62)	29-92				(27)	8-61	22.2	LINAC			(12)	12-15
Landy SFN 2004	U. Miami, Miami, FL	52	58.4	23-83	20 (38.5)	2.6	0.07-12.5	43.4 (37)	14-100	25.0	GKS			(12)	10-14
Wackym ON 2004	Med Col Wisconsin, Milwaukee	32									GKS	27.5	20.3-32.1	13.5	12-14
Chung JNS 2005	Taipei, Taiwan	195	51	11-82	113 (57.9)	4.1	0.04-23.1	36 (31)	1-110	39.0	GKS	(21.9)	17.1-34	(13)	11-18.2
Hasegawa NSGY 2005	Komaki, Japan	317	54	18-79	199 (62.8)	5.6	0.2-36.7	(93)		22.7	GKS	26.2	15-36	13.2	10-18
Myrseth NSGY 2005	Bergen, Norway	103	59.7	22-82	50 (48.5)	2.3	0.4-7.0	70.8	12-170.4	0.0	GKS	35.3	17-40	12.2	10-20
Okunaga JNS 2005	Nagasaki, Japan	46	(60)	21-78	32 (69.6)	(2.3)	0.4-7.0	(56.5)	12-120	26.1	LINAC			(13)	
van Eck JNS 2005	Krefeld, Germany	95	58	23-84		2.3		22	12-42		GKS	(20)		(13)	
Combs IJROBP 2006	Heidelberg, Germany	26	(64)	39-83	18 (69.2)			(110)	30-175	30.8	GKS			(13)	11-20
Friedman JNS 2006	U. Florida, Gainesville	390	(62)	19-88	208 (53.3)	(2.2)	0.2-22.4	40		20.5	LINAC			(12.5)	10-22.5
Hempel EAO 2006	Munich, Germany	123	(59)	19-85	63 (51.2)	(1.6)	0.1-9.9	98	63-129		GKS	(22.7)	15.6-32.5	(13)	10-14.5
Pollock NSGY 2006	Mayo Clinic, MN	46	53.9		19 (41.3)	1.5		42	12-62	0.0	GKS	26.4		12.2	
Chihara AOL 2007	Tokyo, Japan	138	(53)	13-77	61 (44.2)			(60)	6-191	22.5	GKS	29.8	20-40	15.4	10-25.2
Chopra IJROBP 2007	U. Pittsburgh	216	(56.5)	22-88	100 (46.3)	(1.3)	0.008-37.5	(68)			GKS	(26)	20-26	(13)	12-13
Rutten RO 2007	Belgium/Maastricht, The Netherlands	26	63 (67)	30-82	16 (61.5)			(49)	16-85	7.7	LINAC			(12.12)	10-14
Yang JNNP 2008	Seoul Natl. U., South Korea	61	(41)	18-67	41 (67.2)	3.7	0.5-15.5	(53.7)	24.1-102.2	100.0	GKS	24.9	18-28	12.5	9-14
		Total N	3677	Max Range:	10-92		Max Range:	0.008-37.5	Max Range:	1-206		Max Ranges:	12-53		7.5-25.2

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Study ID	Stabilized Disease			Non-CN Complications		Post-RT New Facial Dysfunction		Serviceable Hearing Preservation		Post-RT Improvement in Tinnitus		Post-SRS Surgical Resection						
	Total N	N	% of Reporting	N	%	N	%	N	% of Preop	N	% of Preop	N	%					
Noren AN 1993	254	216	85.0		12	4.7	10	3.9										
Foote IJROBP 1995	36	35	100.0		0	0.0	19	52.8										
Hirato SFN 1996	29	26	89.7		2	6.9	3	10.3										
Kondziolka NEJM 1998	162	153	94.4		3	1.9	22	13.6	15	46.9		4	2.5					
Kwon SFN 1998	88	60	95.2		4	4.5	7	8.0				1	1.1					
Vermuelen SFN 1998	52						6	11.5			3	14.3						
Unger AN 1999	56	53	94.6		1	1.8	2	3.6	16	61.5		2	3.6					
Prasad JNS 2000	153	141	92.2				3	2.0	25	69.4	3	11.5						
Suh IJC 2000	29	28	96.6		2	6.9	7	24.1										
Andrews IJROBP 2001	69				6	10.0			4	33.3								
Bertalanffy AN 2001	41	29	90.6		2	4.9	2	6.3	11	78.6	6	46.2						
Lee SFN 2001	42	39	97.5		1	2.4	1	2.5					0	0.0				
Petit NSGY 2001	47	43	95.6		0	0.0	0	0.0	23	88.5	3	30.0	2	4.3				
Spiegelmann JNS 2001	44	43	97.7		0	0.0	9	20.5	9	69.2		0	0.0	0	0.0			
Karpinos IJROBP 2002	73	50	90.9		3	4.6	3	4.1	4	44.4	5	14.3						
Ottaviani AOHNS 2002	30	26	86.7		0	0.0	0	0.0	10	55.6								
Delbrouck AOLB 2003	95						1	2.1	16	66.7			1	1.1				
Iwai NSGY 2003	51	44	86.3		5	9.8	0	0.0	10	55.6			1	2.0				
Litvack NF 2003	134	117	96.7		4	3.0	3	2.2	29	61.7			3	2.2				
Meijer IJROBP 2003	49				2	4.1												
Rowe JNNP 2003	232	197	92.9		3	1.3	2	0.9	37	75.5			7	3.0				
Chung IJROBP 2004	45				6	13.3	2	4.4										
Landy SFN 2004	52	33	97.1		1	1.9	0	0.0	3	100.0								
Wackym ON 2004	32	30	93.8		8	25.0	0	0.0										
Chung JNS 2005	195	175	93.6		5	2.6	2	1.0	12	60.0								
Hasegawa NSGY 2005	317	279	92.7		22	6.9	5	1.7	52	57.8			5	2.6	6.6			
Myrseth NSGY 2005	103	91	89.2		2	1.9	11	10.8	10	32.3			5	4.9				
Okunaga JNS 2005	46	34	81.0		3	6.8	2	4.8	6	66.7								
van Eck JNS 2005	95	68	87.2				1	1.3	25	83.3	13	16.7	2	2.1				
Combs IJROBP 2006	26				1	3.8	4	15.4	12	70.6								
Friedman JNS 2006	390						17	4.4					4	1.0				
Hempel EAO 2006	123	111	95.7		3	2.4	0	0.0			7	8.3						
Pollock NSGY 2006	46				2	4.3			29	96.7			2	4.3				
Chihara AOL 2007	138						20	16.3										
Chopra IJROBP 2007	216						0	0.0	60	56.6								
Rutten RO 2007	26	25	96.2				0	0.0	10	90.9								
Yang JNNP 2008	61	58	95.1		0	0.0	0	0.0	3	60.0								
Random Effects Model	Rate	95% CI	0.00	0.50	1.00	Rate	95% CI	4.5	3.3-6.1	4.6	3.0-7.0	63.9	57.4-70.0	17.1	10.8-26.0	2.9	2.0-4.0	
Egger's Regression Intercept	Intercept	Std. Error	p-value	1.56	0.46	0.002	Intercept	Std. Error	p-value	-1.56	0.52	0.006	-2.52	0.65	0.0005	1.35	0.66	0.051
Duval and Tweedie's Trim & Fill	Adj. Rate	95% CI	91.1	89.1-92.8		Adj. Rate	95% CI	5.6	4.2-7.6	7.1	4.8-10.4	59.3	51.9-66.4	3.7	2.7-5.3			

Fig. 1 a Summary of demographic and treatment data for vestibular schwannoma. **b** Summary of meta-analysis for vestibular schwannoma. The Forest plot illustrates the relative weight assigned to each study for the calculation of this variable. Other outcome variables

studied using meta-analysis were non-cranial nerve (CN) complications, post-radiation (RT) new facial nerve dysfunction, serviceable hearing preservation, and post-radiation improvement in tinnitus (Forest plots not shown)

0 to 100%, with 16 studies reporting between 20 and 40%. Overall follow-up range was 1–206 months, with cited mean/median follow-up 12–110 months. There was notable variation in dosing parameters with maximal doses ranging 12–53 Gy, and margin doses ranging 7.5–25.2 Gy.

Figure 1b summarizes the meta-analysis for vestibular schwannoma. Response to treatment was defined as ‘stabilized disease’ at last follow-up. This includes tumors that were judged to decrease in size or remain stable. Overall, the rate of reported stabilized disease was 92.2% (95%CI: 90.4–93.7%), with 10 studies not directly reporting results [8, 12, 14, 15, 17, 18, 30, 35, 43, 47???]. However, with significant publication bias, the adjusted rate of stabilized disease was 91.1% (95%CI: 89.1–92.8%). The study reporting control rates with the smallest mean/median lesion volume (1.6 cm³) reported a “stabilized disease” rate of 86.7%, while the study with the largest mean/median lesion volume (7.6 cm³) reported a “stabilized disease” rate of 95.2%. Among those reporting both mean/median lesion volume and rate of “stabilized disease” (14 studies), there was no significant correlation between the two variables (Spearman’s correlation r_s 0.16, $P = 0.59$). The rate of non-cranial nerve complications was 4.5% (95%CI: 3.3–6.1%). With significant publication bias, the adjusted rate was 5.6% (95%CI: 4.2–7.6%). These included hydrocephalus (most common), disequilibrium, refractory edema, cerebellar necrosis, and intratumoral hemorrhage. The overall rate (adjusted for publication bias) of new facial palsy after SRS was 7.1% (95%CI: 4.1–10.4%). The overall rate (adjusted for publication bias) of serviceable hearing preservation was 59.3% (95%CI: 51.9–66.4%). The overall rate in post-SRS improvement in tinnitus was 17.1% (95%CI: 10.8–26.0%), though only 7 studies reported quantifiable comparative pre- and post-treatment tinnitus rates. Overall, the rate of surgical resection after SRS treatment was 3.7% (95%CI: 2.7–5.3%) after adjustment for publication bias.

In the case of vestibular schwannoma, qualitative changes in dosing parameters have generally reduced the dose applied in response to early concern in the literature regarding complication rates. In order to understand the potential effect of changing dosing parameters, we analyzed outcomes in relation to dose. Pearson’s correlation evaluation of the rate of facial nerve palsy against the maximal margin dose used demonstrated a strong significant positive correlation (r 0.52, P 0.0035). However, there was no significant correlation between maximal margin dose and rate of disease stabilization (r 0.01, P 0.95).

Glioblastoma

Of 21 studies screened, 11 met inclusion criteria [5, 94–103], while 10 were excluded [104–113]. The most common reason for exclusion was the use of fractionation (5 studies)

[104, 106, 111–113]. Nine studies were classified as class III evidence, while 2 studies were classified as class II evidence; one was a case–control study and one was a prospective randomized study [98, 102]. The prospective, randomized study was determined not to meet strict criteria for class I evidence based on the following criteria: (1) The trial was not blinded or masked in outcome assessment. (2) While there was no initial cross-over, a significant number of patients underwent salvage therapy. An intention-to-treat analysis was used to determine effect; while this is a valid method, there was no discussion of the bias of salvage therapy, especially for a number of patients originally allocated to non-radiosurgery who received salvage radiosurgery. (3) While baseline characteristics of the population were presented in the publication, no statistical comparisons were made to ensure a statistically matched controlled cohort for comparison. Figure 2a summarizes demographic and treatment data. About 456 patients were included; sample sizes ranged 5–89. Age ranged 3–85 years, while cited mean/median ages were 43–59 years. Overall follow-up range was 1–61 months, with cited mean/median follow-up 8–61 months. One study utilized the Radiation Therapy Oncology Group (RTOG) Protocol 9005, a tumor size-related dose determination protocol, in setting their dose parameters [102, 114].

Figure 2b summarizes the outcome analysis. There was significant variability in the way in which data were accumulated and presented. Of the 11 studies included, 6 represented case series summarizing the experience of SRS as adjuvant or salvage treatment of GBM, while 5 directly compared treatment with SRS to a designated comparison group. Overall, median survival for patients treated with conventional therapy with adjunctive SRS was 9.5–26 months. In publications directly comparing SRS to control or alternative treatment groups, median survival for SRS from time of diagnosis was 13.5–26 months, while for comparison groups it was 13–23 months. Among publications reporting, 2-year survival for patients receiving SRS was 19–53%. Survival rates could not be quantitatively evaluated due to heterogeneity of application (as adjuvant therapy or as salvage after progression/recurrence). A comparison of median survival rates of studies in which SRS was used as a boost adjunct to initial therapy [95, 99, 100, 102, 103] versus studies in which SRS was used as salvage therapy for recurrent tumor [94, 96, 98, 101], the ranges of median survival were similar (9.5–25 months vs. 10.2–26 months, respective). Overall complication rate from SRS was 11.4% (95%CI: 5.1–23.6%) without significant publication bias.

Meningioma

Of 23 screened studies, 15 studies met inclusion criteria [7, 115–128], while 8 were excluded [129–136]. The most

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Study ID	Group	Class	Total N	Age		Female - N(%)	Previous Resection - N(%)	Follow-up (months)		Modality	Maximal Dose (Gy)		Margin Dose (Gy)	
				Mean (Median)	Range			Mean (Median)	Range		Mean (Median)	Range	Mean (Median)	Range
Chamberlain Cancer 1994	UCSD, San Diego	III	5	(43)	17-62		5 (100)	(8)	2-29	LINAC		(12.1)	12-13.5	
Masciopinto JNS 1995	U Wisconsin, Madison	III	31	(57.7)	20.4-78.6	9 (29.0)	20 (64.5)	12.8 (9.5)	3-37.8	LINAC	15-35	11.7	10-20	
Shrieve NSGY 1995	BWH, Boston, MA	III	86	(46)	9-77	33 (38.4)		(17.5)	6.8-45.1	LINAC		(13)	6-20	
Whang JKMS 1995	Seoul, Korea	III	12	43	4-58	5 (41.7)	9 (75.0)	(10)	3-26	GKS		(12.8)	10-25	
Kondziolka NSGY 1997	U Pittsburgh	III	64	51	3-72		41 (64.1)			GKS	30.5	21.4-50	15.5	12-25
Nwokedi NSGY 2002	U Maryland, Baltimore	III	31	(50.4)	6-85		21 (67.7)	(17.5)		GKS		(17.1)	10-28	
Cho TCRT 2004	U Minnesota, Minneapolis	III	14	(50)	14-89	7 (50.0)	8 (57.1)	(12.1)	3.9-53.9	LINAC		(10.5)	10-18	
Souhami IJROBP 2004	Multicenter	II	89	56.4	18-79	33 (37.1)	80 (89.9)	(81)		GKS/LINAC	**	**	**	
Combs Cancer 2005	Heidelberg, Germany	III	32	(56)	33-76	13 (40.6)	28 (87.5)	(10)	1-25	LINAC		(15)	10-20	
Hsieh NSGY 2005	Northwestern U, Chicago	III	51	(59)	17-81	23 (45.1)	46 (90.2)	(21)	5-56	GKS	(24)	15-32	(12)	
Mahajan JNS 2005	MD Anderson, Houston	II	41	(54)	17-69	14 (34.1)	37 (90.2)	(21)	3-61	LINAC				
Total N			456		Max Range: 3-85		57.1-100%		Max Range: 1-61		Max Ranges: 15-50		6-28	

B

Study ID	Total N	Protocol and Comparison Group	Survival Analysis				Complications				
			Median Survival (mos)	Comparison Group	Comparison Group Median Survival (mos)	SRS 2-year Survival (%)	Comparison Group 2-year Survival (%)	N	%		
Chamberlain Cancer 1994	5	Recurrent after conventional therapy	15	None				2	40		
Masciopinto JNS 1995	31	Part of primary treatment with conventional therapy	9.5	None							
Shrieve NSGY 1995	86	Recurrence/progression after conventional therapy	10.2*	Brachytherapy (N=32)	11.5*	19	17	26	30.2		
Whang JKMS 1995	12	Adjuvant to conventional therapy	12	None							
Kondziolka NSGY 1997	64	Adjuvant or progression after conventional therapy	26	None		51		1	1.6		
Nwokedi NSGY 2002	31	Adjuvant to conventional therapy	25	Conventional - surgery/EBRT (N=33)	13			2	6.5		
Cho TCRT 2004	14	Recurrent after conventional therapy	16	ISRT (N=10)	15.9			4	28.6		
Souhami IJROBP 2004	89	Adjuvant to conventional therapy	13.5	Conventional - surgery/EBRT (N=97)	13.6	21	19	11	12.4		
Combs Cancer 2005	32	Recurrent after conventional therapy	22	None		49		0	0		
Hsieh NSGY 2005	51	Adjuvant to surgery/EBRT or recurrence	14.3	None		30		0	0		
Mahajan JNS 2005	41	Recurrent/progressive after conventional therapy	26	Conventional - surgery/EBRT (N=41)	23	53	49				
Total N			456		Ranges	9.5-26	13.6-23	19-53	17-49		
									Random Effects Model	Rate	11.4
									Egger's Regression Intercept	95% CI	5.1-23.6
										Intercept	-2.28
										Std. Error	1.04
										p-value	0.07

Fig. 2 a Summary of demographic and treatment data for vestibular schwannoma. In one study, treatment doses were based on RTOG Protocol 9005 (marked with **). b Summary of analysis for glioblastoma multiforme (GBM). Median survival was considered the primary outcome endpoint, which ranged among included studies 9.5–26 months for patients receiving SRS. Given the heterogeneous inclusion criteria and comparison groups, statistical meta-analysis of

median survival could not be performed on the entire group. However, 2-year survival rates for patients receiving SRS ranged from 19 to 53 months, while in similar comparison groups not receiving SRS, they ranged from 17 to 49 months. One study reported median survival from time of SRS rather than from time of diagnosis (marked with *)

common reason for exclusion was publication from a group with an already included study (3 studies) [130, 135, 136]. All included studies were case series, representing class III evidence. Figure 3a summarizes demographic and treatment data. About 2,734 patients were included, and sample sizes ranged 24–982. Age ranged 8–90 years, while cited mean/median ages ranged 47.8–60 years. Tumor volumes varied widely with a maximum range of 0.11–121.8 cm³; median volume range was 4.1–13.8 cm³. Overall follow-up range was 3.96–144 months, and cited mean/median follow-up ranged from 26 to 94.8 months. About 77.1% of tumors were anatomically classified as “skull base.” The proportions of patients receiving SRS as the primary treatment modality ranged from 0 to 78.3%. Histology was not available for all treated tumors. However, among those reporting histology, the proportion of patients with benign tumors ranged from 77.5 to 100%.

Figure 3b summarizes the meta-analysis for meningioma. Tumor response was defined as “stabilized disease” if there was no change or decrease in size at last follow-up.

Overall, the rate of reported stabilized disease was 89.0% (95%CI: 84.6–92.3%), with one study not directly reporting results of number of tumors stable or decreasing in size [126]. However, that study reported an overall control rate of 88.0% at a mean follow-up of 39 ± 18 months [126]. Regarding tumor volume, the study reporting control rates with the smallest median lesion volume (4.1 cm³) reported a “stabilized disease” rate of 97.2%, while the study with the largest median lesion volume (13.8 cm³) reported a “stabilized disease” rate of 85.2%. However, among those studies reporting both median lesion volume and rate of “stabilized disease” (10 studies), there was no significant correlation between the two variables (Spearman’s correlation *rs* -0.29, *P* = 0.42). Overall complication rates were 7.0% (95%CI: 5.3–9.3%). These included trigeminal dysfunction, diplopia, seizures, hypopituitarism, gait instability, prolonged symptomatic edema requiring treatment, and decreased visual acuity. The longest reported local control rate was 95% at 10 years in 22 of 982 followed for that interval [124].

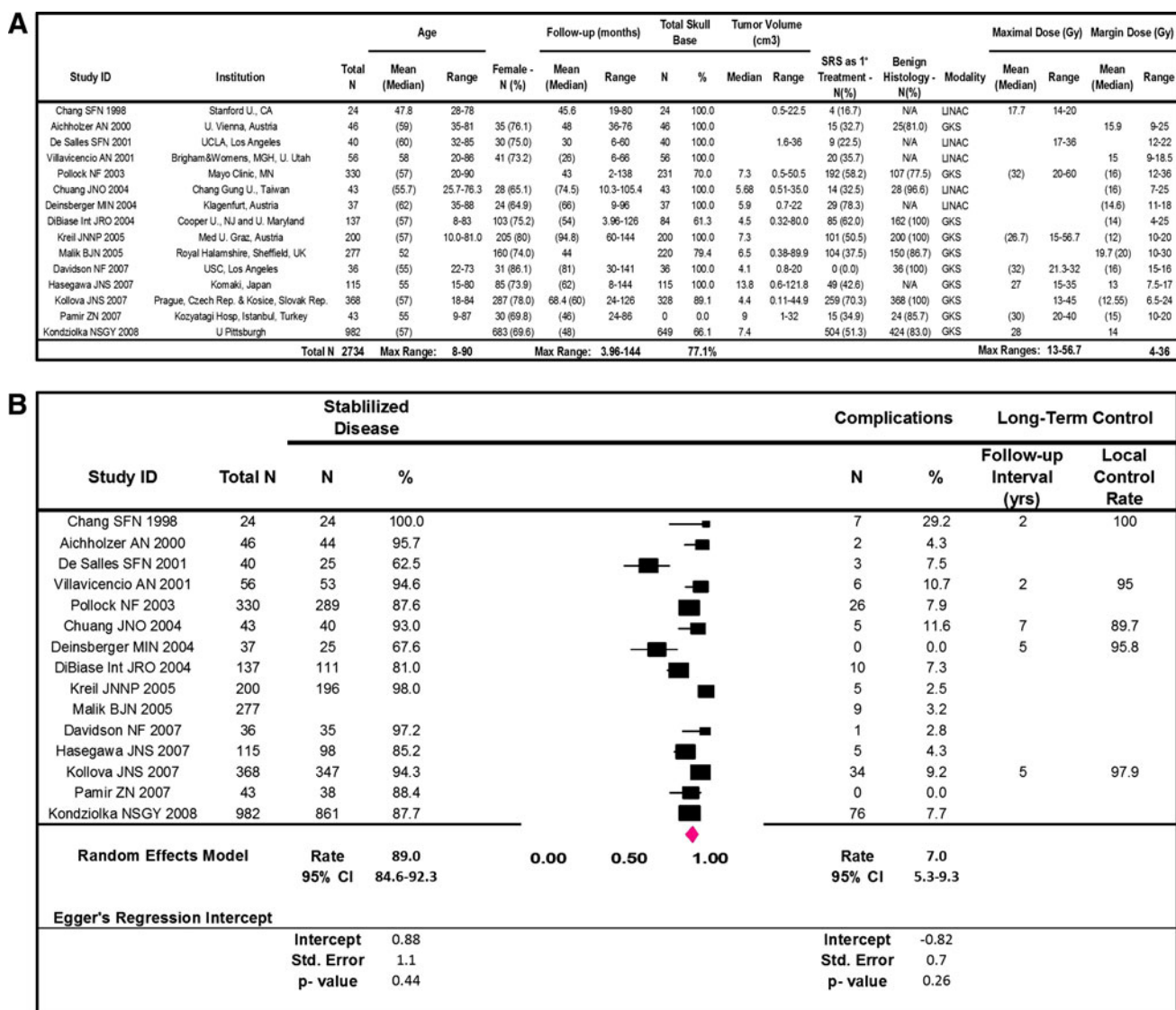


Fig. 3 a Summary of demographic and treatment data for vestibular schwannoma. b Summary of meta-analysis for meningioma. Of those studies directly reporting disease stabilization, the overall rate was 89.0%. The Forest plot illustrates the relative weight assigned to each

study for the calculation of this variable. A small group of studies detailed long-term follow-up rates of local tumor control, which varied from 89.7–100%

Metastases

Of 57 studies screened, 27 studies met inclusion criteria [137–163], while 30 were excluded [114, 164–192]. The most common reasons for exclusion were publication from a group with an already included study, and application of radiosurgery as an adjunct rather than primary treatment. Publications describing SRS as a boost for other treatment were included if SRS was part of the original treatment plan. In one study, SRS for single brain metastases was compared to a protocol in which the tumor with an additional 2 mm margin was targeted with radiosurgery; as this protocol represented a non-conventional practice, only the patients that underwent the conventional protocol were

included [138]. Twenty-five included studies were case series, representing class III evidence. Two studies were randomized, controlled, nonblinded comparison of SRS to another modality; one compared SRS to surgery and WBRT, while another compared SRS alone to SRS in combination with planned WBRT [146, 155]. In providing detailed information regarding screening and inclusion, as well as control of baseline characteristics, both represented class I evidence. One studied only patients treated with single metastases [155], while the other included patients with 1–4 metastases [146]. Figure 4a summarizes demographic and treatment data. About 2,679 patients were included, and sample sizes ranged from 22 to 502. Age ranged 16–92 years, while cited mean/median ages ranged

A

Study ID	Group	Study Goal/Inclusion Criteria	Class	Total N		Age				Single Mets - %	WBRT - N(%)	Tumor Volume (cm ³)		KPS		Maximal Dose (Gy)		Margin Dose (Gy)	
				Patients	Lesions Treated	Mean (Median)	Range	Female - N(%)	Mean (Median)			Range	Median	Range	Modality	Mean (Median)	Range	Mean (Median)	Range
Mori JROBP 1998	U Pittsburgh	Melanoma mets treated with SRS	III	60	118	49.1	16-79	15(25.0)	30.5	45(75.0)	3.0	0.1-25.5	90	50-100	GKS		16.4	10-20	
Amendola Cancer 2000	Coral Gables, FL	RCC mets treated with SRS	III	22	38	(60)	38-80	8(36.4)	10.5	11(50.0)	3.9	0.1-75.5	80	50-90	LINAC	(18)	15-22		
Firik ASO 2000	U Pittsburgh	Breast mets treated with SRS	III	30	58	55	39-70	28(93.3)	24.1	26(86.7)		0.1-15.1			GKS		12-20		
Simonova RO 2000	Prague, Czech Rep.	Solitary brain mets treated with SRS	III	237	237	(56.4)	35-77	105(44.3)	100	4(1.7)			70	40-100	GKS		(21.5)	16-30	
Sanghavi JROBP 2001	Multi-institutional	Mets treated with WBRT and SRS boost to all visible lesions	III	502		(59)	26-83	241(48.0)		502(100)			80	>70-100	GKS/LINAC				
Hoshi IJU 2002	Sendai, Japan	Mets (one or multiple) treated with SRS	III	42	110	63	36-80	11(26.2)	20	0			90	20-100	GKS		(25)	20-30	
Jawahar SFN 2002	LSU, Shreveport	Mets treated with SRS without WBRT	III	61	103	57	36-81	26(42.6)	26.2	18(29.5)	9.7	0.5-33			GKS		15	11-21	
Sheehan JNS 2002	U Pittsburgh	NSCLC mets treated with SRS	III	273	627	61.3 (62)	35-85	150(54.9)		214(78.4)	2.9 (5.4)	0.07-52.3	90	50-100	GKS	(33)	18-45	(16)	11-22.5
Shinoura JNO 2002	Tokyo, Japan	Mets treated with SRS vs surgery/WBRT	III	28	52	55	28-81	15(30.6)	23.1	0	(1.6)	0.02-10.4			LINAC	28.9	20-35	23.7	15-25
Hasegawa SN 2003	U Pittsburgh	GI mets treated with SRS	III	39	72	63.1	40-79	13(33.3)	34.7	32(82.1)	4.9	0.1-18.7	90	50-100	GKS	30.9	20-40	16.6	11-20
Noel LC 2003	Groupe Pile Salpetriere, Paris	Lung mets - SRS/WBRT vs SRS alone - SRS/WBRT arm	III	22	22	57 (56)	43-76	8(27.3)	72.7	22(100)	3 (1.2)	0.06-15.7	>70	80-100	LINAC	16.5(15.4)	13.6-25.5	10.5(10.3)	6-16.1
Noel LC 2003	Groupe Pile Salpetriere, Paris	Lung mets - SRS/WBRT vs SRS alone - SRS alone arm	III	34	51	59 (60)	35-78	14(41.2)	60.8	0	2.9 (2.0)	0.02-16.4	>70	60-100	LINAC	21(20.3)	14.2-36.7	14.5(14.4)	10.6-15.6
Sheehan JNS 2003	U Pittsburgh	RCC mets treated with SRS	III	69	146	60	42-83	21(30.4)		36(52.2)	(2.8)	0.09-35	80	50-100	GKS	(32)	20-40	(16)	12.5-20
Combs SO 2004	Heidelberg, Germany	Breast mets treated with SRS without WBRT in different	III	62	103				13.6	52(83.9)					LINAC				10-20
Datta AJCO 2004	LSU, Shreveport	Mets treated with WBRT vs SRS	III	53		(57.5)	36-79	22(41.5)		12(22.6)		< 30		GKS		(16)		13-19	
Muacevic Cancer 2004	Munich, Germany	Breast mets treated with SRS	III	151	620	(60)	35-78	148(98.0)	9	46(30.5)	(2.2)	0.1-20.9	80	40-100	GKS	37(36)	26-47	19(18)	10-36
Muacevic MIN 2004	Munich, Germany	Mets from RCC treated with SRS alone	III	85	134	(60)	35-78	28(30.6)	22.4	0	(1.2)	0.1-14.2	80	50-100	GKS	39(38)	28-57	21(21)	15-35
Ulm NSGY 2004	U Florida, Gainesville	Mets treated with SRS	III	383	642	59	29-86	186(48.6)	37.5	252(65.8)	(5.5)				LINAC		(15)	10-22.5	
Goyal JNS 2005	Howard U., Washington, DC	Breast mets treated with SRS	III	43	84	51 (48)	32-92	43(100)	20.2	30(69.8)	4.1 (1.5)	0.31-20.5	90	40-100	GKS	51.2(51.4)	24.9-67.4		
Koc JNO 2005	OSU, Columbus	Melanoma mets treated with SRS	III	26	72	52.7 (54)	36-80	11(42.3)	13.9	14(53.8)	(1.7)		90	70-100	GKS	(25.6)	10-40	(18)	8-22
Manon JCO 2005	Multi-institutional	RCC melanoma, sarcoma mets treated with SRS	III	31	47			4(12.9)	38.3	0					GKS/LINAC				15-24
Aoyama JAMA 2006	Sapporo, Japan	RCT - SRS/WBRT vs SRS alone - SRS/WBRT arm	I	65	96	62.5	36-78	19(29)	32.3	65(100)					70-100			16.6	18-25
Aoyama JAMA 2006	Sapporo, Japan	RCT - SRS/WBRT vs SRS alone - SRS alone arm	I	67	114	62.1	33-86	14(20.9)	28.9	0					70-100			21.9	18-25
Deinsberger JNO 2006	St. Pölten, Austria	Mets treated with SRS	III	110	161	(58)	38-81	43(39.1)	42.5	35(31.8)	(3.1)	0.3-15	80	70-100	LINAC			18(18.3)	11-22
Flannery JROBP 2008	U Maryland & Konrad, Baltimore & Loyola	Synchronous NSCLC mets treated with SRS	III	42	42	(58)	38-74	15(35.7)	100	33(78.6)			90	70-100	GKS			(18)	
Kased JNO 2008	UCSF, San Francisco	Mets treated with SRS	III	42	44	(55)	25-79	22(52.3)	11.4	24(57.1)	(0.3)	0.015-2.9	90	40-90	GKS	(31.4)	17.8-40.0	(16)	10.1-19.8
Monaco Cancer 2008	U Pittsburgh	Ovarian and endometrial mets treated with SRS	III	27	27	60.4			100	18(66.7)			90		GKS				
Muacevic JNO 2008	St. Anne Hospital, Paris	RCT - Surgery/WBRT vs SRS alone - SRS arm	III	31	51	54.3 (55)	35-78	19(61.3)	100	0			70-100	GKS	41	28-54	21	14-27	
Nataf JROBP 2008	St. Anne Hospital, Paris	Single met SRS vs SRS +2mm margin - SRS arm	III	42	42	(61)	31-80	10(23.8)	100	9(21.4)	2.0		80	50-90	LINAC	25.4		15.8	
				Total N	2679		Max Ranges	16-92			0-100			20-100			10-67.4		6-35

B

Study ID	Total N	Comparison Group (non-SRS)	Survival Analysis										Reported Local Control Rate (%)	Complications					
			Median Survival (mos)	Median Survival (mos)	Pathology Specific Median Survival			Renal Cell	SRS 1-year Survival (%)	Nonneurologic Death		N		% of Known Causes of Death	N	%			
					Lung	Breast	Melanoma			N	% of Known Causes of Death								
Mori JROBP 1998	60		7								35	79.5	90	3	5				
Amendola Cancer 2000	22		8.4								18	85.7	91.1	1	4.5				
Firik ASO 2000	30		13			13					8	61.5	93						
Simonova RO 2000	237										149	81.9	91.1	37	15.6				
Sanghavi JROBP 2001	502	WBRT alone	10.7																
Hoshi IJU 2002	42		12.5																
Jawahar SFN 2002	61		6						12.5					91					
Sheehan JNS 2002	273		7								23	57.5	73.8						
Shinoura JNO 2002	28	Surgery/WBRT	8.2*	34.4*							134	57.8	84	21	7.7				
Hasegawa SN 2003	39		5											59.6					
Noel LC 2003 - SRS/WBRT	22		14			14					21	51.2							
Noel LC 2003 - SRS alone	34		7			7								83.6	2	5.1			
Sheehan JNS 2003	69		6								57	95	96	4	5.8				
Combs SO 2004	62		15			15								89	2	3.8			
Datta AJCO 2004	53	WBRT alone	6								72	70.6	94	26	17.2				
Muacevic Cancer 2004	151		10			10					47	78.3	94	11	12.9				
Muacevic MIN 2004	85		11.1						11.1		45	47	94	2	0.5				
Ulm NSGY 2004	383		9																
Goyal JNS 2005	43		13			13													
Koc JNO 2005	26		6						6		25	9	56.3	1	3.8				
Manon JCO 2005	31		8.3								9	42.9	67.8	17	54.8				
Aoyama JAMA 2006 - SRS/WBRT	65		7.5								38.5	44	77.2	11	16.9				
Aoyama JAMA 2006 - SRS alone	67		8								50	80.6	84	11	16.4				
Deinsberger JNO 2006	110		12.5								54.9	80	70.0	3	2.7				
Flannery JROBP 2008	42		18			18					15	75							
Kased JNO 2008	42		9								12	63.2	61.5	4	9.5				
Monaco Cancer 2008	27		5								15			2	7.4				
Muacevic JNO 2008	31	Surgery/WBRT	10.3	9.5									96.8	18	58.1				
Nataf JROBP 2008	42	Lesion+2mm margin	11.3	19										3	7.1				
				Total N	2679		Ranges	5-14			7-14	10-15	6-7	6-12.5	15-54.9			59.6-96.8	
														Random Effects Model	Rate	10.0			
														Egger's Regression Intercept	95% CI	6.4-15.3			
															Intercept	-2.2			
															Std. Error	1.2			
															p-value	0.09			

Fig. 4 a Summary of demographic and treatment data for vestibular schwannoma. **b** Summary of meta-analysis for intracranial metastatic disease. * Indicates survival intervals were reported as means rather than as medians for that study [152]. # Indicates that survival data were listed in reference to time from diagnosis rather than time from

treatment [157]. Given this confounding factor, survival results from this study were not included in the summary ranges. Primary endpoints were median survival (range 5–14 months), 1-year survival rates (15–54.9%), and reported local disease control rates (59.6–96.8%)

49.1–63.1 years. The percentage of treated lesions that represented single intracranial metastases varied considerably; while 5 studies only reported patients in whom a

single lesion was treated, the percentage ranged in other studies from 9.0 to 72.7%. In 7 studies, WBRT was not administered to any patient in the study group; however,

among other studies, this rate varied from 1.7 to 100%. Most patients were relatively high-functioning, with median KPS 70–90 among included studies. Tumor volumes varied widely with a maximum range of 0.015–75.5 cm³; mean/median range was 0.3–9.7 cm³.

Figure 4b summarizes the results of the analysis. Of note, there was significant variability in the pathologies studied. Of 27 included studies, 13 evaluated specific primary oncologic pathologies, while the remaining studies published grouped results of several types of primary pathology. Overall, median survival for patients treated with SRS as part of the primary therapeutic treatment plan ranged from 5 to 14 months from the time of SRS treatment. One study reported only survival intervals from time of diagnosis; while illustrated in Fig. 4b, the results were not included in the data synopsis [157]. One-year survival rates varied significantly with a 15–54.9% range. Among pathology-specific publications, melanoma had the lowest range of median survival at 6–7 months, while breast carcinoma had the longest reported pathology-specific median survival of 15 months. Among known causes of death from studies reporting cause of death, the rate of completely nonneurologic deaths (most often due to progression of systemic disease) ranged from 42.9 to 95%. About 17 of 27 studies reported local tumor control rates, and demonstrated a relatively high range of 59.6–96.8%, with 9 of 17 reporting $\geq 90\%$ local control after SRS. Regarding tumor volume, the study reporting control rates with the smallest mean/median lesion volume (0.3 cm³) reported a local tumor control rate of 61.5%, while the study with the largest mean/median lesion volume (9.7 cm³) reported a local tumor control rate of 73.8%. However, among those studies reporting both mean/median lesion volume and local tumor control rates (11 studies), there was no significant correlation between the two variables (Spearman's correlation $r_s -0.06$, $P = 0.85$). Among those reporting, overall complication rate was 10.0% (95%CI: 6.4–15.3%) without significant publication bias. Complications included hemorrhage, seizures, symptomatic radiation necrosis, hearing loss, and new neurological deficits (hemiparesis, visual field deficits).

Discussion

SRS has become an important tool in the armamentarium of physicians who treat neuro-oncologic diseases. Representing a marriage between SRS, neuroimaging and radiation biology, SRS allows the treating physician to focally target the lesion while limiting the exposure to vital anatomy [193]. With dose optimization and an understanding of dose tolerances [194], SRS has become a highly-effective minimally invasive method for addressing focal neuro-oncologic disease.

Vestibular schwannoma (VS) represents the most extensively studied disease to which SRS is applied as a standalone treatment. A typically benign tumor, mass effect from continued growth often causes the most morbidity. Characteristically impairing hearing and balance first (as tumor-related mass effect is exerted on the vestibulocochlear nerve branches), further growth may cause facial motor dysfunction (via the facial nerve), brainstem dysfunction, and hydrocephalus. Among 37 studies, the adjusted efficacy of SRS in stabilizing VS was 91.1%. While smaller volume did not appear to correlate with tumor control, the overall range of mean/median tumor volumes reported was 1.3–7.6 cm³. This reflects the general practice that vestibular schwannomas ≤ 3 cm in diameter may be considered for radiosurgery, although no randomized controlled studies have firmly established size as a limiting factor. Complication and deterioration rates related to SRS treatment remain low; post-radiation facial dysfunction was 7.1%, while non-cranial nerve complications were 5.6%. Hearing preservation is an important issue for those with VS discovered prior to the unilateral loss of hearing; with an overall preservation rate of 59.3%, SRS offers an efficacious tool in treating VS with a measureable rate of hearing preservation. There is some evidence to suggest hearing preservation rates may be higher in SRS-treated patients compared to those undergoing surgical resection [24, 195]. Finally, some recently presented abstracts and research suggest that low-dose fractionated stereotactic radiotherapy may have comparable control rates to high-dose, while improving hearing-preservation [196]. This raises the question of whether fractionated radiotherapy is better than single-dose radiosurgery for hearing preservation; while further research is needed, limited class III evidence suggests they may be comparable [197]. However, SRS is not a panacea for all lesions. The effects of SRS are not immediate; patients requiring rapid decompression of mass effect from large tumors will achieve faster results through microsurgery. While only reported in 7 studies, the rate of response to SRS of tinnitus was poor (17.1%). Though the overall effect on quality of life of persistent tinnitus may be variable [198], it represents an important limitation to SRS as a treatment tool for this disease. The effect on tinnitus may represent an important limitation to SRS, as these results do not compare favorably for post-operative rates in studies evaluating the effects of microsurgical excision. Such studies have reported rates of tinnitus improvement from 16 to 62% [198–200].

Glioblastoma (GBM) is the most malignant primary intracranial tumor. Survival from diagnosis ranges from 12 to 24 months, and no treatment regimen has been established to reliably significantly extend long-term survival. Extent of initial surgical resection has been shown to provide a significant survival benefit, and regimens of

radiotherapy, brachytherapy, and chemotherapy have been evaluated as adjuvant therapy for GBM [201]. SRS offers an additional tool for targeted radiation of GBM. Published studies offer some guidance, but most clearly demonstrate the variability with which SRS has been employed. Initial experience with SRS as an adjunct tool suggested a beneficial role in upfront treatment of high-grade gliomas [109]. However, of the examined literature, the study by Souhami et al. [102] is often cited as evidence of no significant benefit of SRS in GBM. Several study limitations preclude the study from defining the role or lack thereof for SRS in GBM treatment. First, of the 96 patients in the control (non-SRS) group, 18 (19%) underwent “salvage therapy” with SRS [102]. Despite the equivocal findings of the effects of SRS on survival, it was used as a modality for salvage therapy in the non-SRS group, reflecting unincorporated “cross-over” among the two study groups. Other studies have shown more favorable results of SRS. Compared to those receiving conventional therapy (surgery, EBRT), Nwokedi et al. [100] demonstrated that those ($N = 31$) undergoing adjuvant SRS demonstrated high relative median survival (25 months versus 13 months). As such, the overall role for SRS in management of GBM has yet to be defined.

Meningiomas are focal lesions arising from the dura that cause neurological symptoms by local mass effect. Although a small percentage of tumors are classified as atypical or anaplastic, the majority are benign. However, because of their dural origin, they may arise in very accessible locations such as the cerebral convexities, or in surgically difficult skull base regions such as the petroclival apex, medial sphenoid wing, or cavernous sinus. SRS has become a tool primarily used for adjuvant therapy of meningiomas that have undergone previous resection, particularly for histologically atypical or anaplastic tumors. For challenging skull base tumors, SRS may be used to treat small amounts of disease intentionally left during resection to prevent injury to vital neurovascular structures [202]. Among 2,734 patients, 77.1% were classified as ‘skull base’; in 9 studies, SRS was used as the primary treatment in less than 50% of patients. This distribution underscores the importance of SRS as a tool in treating residual skull base tumors after resection. As a tool in treating meningiomas, SRS has an overall stabilization rate of 89.0%, with a low complication rate of 7%. Among studies reporting tumor volumes, ranges varied significantly (0.11–121.8 cm³). While no study specifically evaluated volume in a controlled fashion, among those reporting volume and control rates, there was no significant correlation. This result should be interpreted with caution, however, as other potentially important variables were not controlled across the evaluated studies. DiBiase et al. [121] evaluated prognostic factors associated with SRS treatment

for benign intracranial meningiomas in 162 patients. In a multivariate analysis, gross tumor volume >10 cm³ was associated with significantly lower disease-free survival (hazard ratio 4.58, $P = 0.05$). As SRS is increasingly employed as a primary and adjunctive treatment tool for meningiomas, particularly of the skull base, more rigorous controlled studies will be required to more clearly elucidate size parameters for treatment. However, with such rates of disease stabilization, SRS clearly has a role for treatment of meningiomas, especially those small in size [124].

The most common intracranial tumor is a metastatic lesion of extracranial primary oncologic pathology. About 15–30% of patients with cancer develop intracranial metastases [203, 204]. Management strategies necessitate a coordinated effort with oncologists to confront the systemic disease, and to minimize further intracranial metastases. Treatment strategies for intracranial lesions have included surgery, WBRT, and, more recently, SRS [155, 205, 206]. However, the specific role of SRS for cerebral metastases has not been well-defined. In a review of radiosurgery applications for metastatic disease in 2005, McDermott and Sneed concluded that SRS with WBRT remains a treatment option for brain metastases. However, the appropriateness and efficacy of SRS depends upon several factors including the systemic-disease status, number of metastases, location, and patient status (KPS) [207]. These variables, along with the varying types of primary pathology, complicate attempts to form singular recommendations for the application of SRS to metastatic disease. The analysis conducted herein demonstrates this difficulty, as the variances in survival rates after SRS depend upon pathology, as well as upon the scenario of application. First, underlying pathology affects survival; the notable differences in median survival among studies publishing on singular underlying primary diagnoses demonstrate this. While overall median survival ranged from 5 to 14 months from time of treatment, the two studies reporting only melanoma patients represented the lowest median survivals of 6 and 7 months [148, 159]. Future studies that evaluate management of intracranial disease should publish not only overall results, but note pathology-specific outcomes. Second, despite the varying pathologies studied, local control rates of treated lesions were relatively high (59.6–96.8%), with the majority of reporting studies demonstrating rates $\geq 90\%$. The lowest reported local control rate was 59.6% among 28 patients treated with SRS without any other modality [152]. In this study, only 23.1% of lesions treated were single metastases, and a high proportion of the underlying primary pathology was colon carcinoma (25% of lesions treated) [152]. Hasegawa et al. [158] suggested that higher radiosurgical doses for gastrointestinal metastases may be required when they reported lower local control rates in their series in comparison to published control rates in other primary pathology

metastases. A second complicating factor is the context in which SRS is applied. While some studies evaluated SRS alone, other studies reported results of patients treated with SRS, WBRT, surgery, and/or chemotherapy. Some studies evaluated SRS results in the context of controlled systemic disease, while others did not address the primary oncology. Furthermore, volume parameters for using SRS varied widely (0.015–75.5 cm³). Thus, the data presented, while providing an overall set of published benchmarks, is subject to significant population- and treatment-based variables which obviate quantitative meta-analysis of the results. Recent publication of a set of guidelines and recommendations for treatment of metastatic brain tumors by the Joint AANS/CNS Section on Tumors helps elucidate the current role for SRS [208]. In their publication on SRS, the group found level-1 evidence supporting the use of SRS with WBRT compared to WBRT alone for single lesions in high-function patients (KPS \geq 70). They found level-2 evidence supporting SRS plus WBRT for 1–4 lesions, supporting equivalence of single-dose SRS alone versus single-dose SRS plus WBRT, and supporting equivalence of surgical resection plus WBRT and SRS plus WBRT in selected patients. Our results do not contradict the conclusions of these treatment guidelines. Rather, our analysis emphasizes the local control rates seen with SRS, affirming the conclusions of this Joint Section report. Furthermore, we highlight the importance of systemic disease control, noting the apparent incongruity of high local control rates and low median survival.

The application of SRS to other neuro-oncologic pathologies has been studied in smaller series. SRS has been used in pituitary tumor pathology, both to treat secreting and nonsecreting tumors. Jane et al. [6] reported their results treating 220 hypersecreting pituitary adenomas with gamma knife; biochemical remission occurred in 73% of Cushing disease, 36% of growth hormone-secreting tumors, 14% of Nelson syndrome, and 11% of prolactinomas. Furthermore, SRS may be effective in treating previously irradiated pituitary adenomas. Swords et al. [209] found that linear accelerator treatment in 21 patients who had previously undergone 45–50 Gy conventional radiotherapy resulted in significant reductions in abnormal hormone secretion in GH-secreting adenomas. In regard to endocrine-inactive pituitary adenomas, SRS may have a significant role in controlling tumor growth; a review by Witt [210] of published series demonstrated growth control of nonfunctioning pituitary adenomas ranging between 92 and 100%.

SRS has also been evaluated in the treatment of other intracranial oncologic pathologies. Kobayashi et al. [211] studied gamma knife treatment in 107 patients with craniopharyngioma with long-term follow-up (mean 65.5 months). While complete response was observed in

only 19%, tumor control rate was 77%, with a progression rate of 23%. Deterioration in neurological and pituitary-hypothalamic symptoms was observed in only 16.5% after SRS treatment. Chung et al. [212] also reported SRS results in treating 31 patients with craniopharyngioma; at mean follow-up of 36 months, tumor control was achieved in 87% with 1 patient suffering new visual field restriction, and none with treatment-related endocrinological impairment. Sheehan et al. [213] found that SRS resulted in tumor stabilized or regression in 88% of 26 patients with trigeminal schwannoma. SRS has also been studied as a treatment for hemangiopericytomas, brainstem gliomas, oligodendrogliomas, recurrent medulloblastomas, juvenile pilocytic astrocytomas and low-grade astrocytomas [214–220]. Further studies are needed to fully elucidate the role of radiosurgery as a tool for treating these intracranial pathologies.

Conclusion

Over the past two decades, SRS has rapidly developed into a vital treatment tool in neuro-oncology. Thorough review of its neuro-oncologic applications demonstrates several important principles. The majority of evidence supporting SRS is class III. Clearly, there is a need and an opportunity for future well-designed clinical trials to evaluate SRS for specific neuro-oncologic diseases. Despite the evidence class, extensive numbers of studies support the role of SRS in treating small meningiomas of the skull base, as well as vestibular schwannomas in which tinnitus is not a major symptom. Small intraparenchymal metastases can be locally controlled with SRS, though the effect is clearly somewhat dependent on primary pathology. Finally, the role for SRS in treating glioblastoma and other high-grade intraparenchymal tumors is less defined, and further studies are clearly needed. Given its relative minimally invasive nature, further advancement of SRS as a tool in neurosurgery and radiation oncology to address intracranial oncologic pathologies will undoubtedly occur.

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