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REVIEW ARTICLE

Cranial Stereotactic Radiosurgery: Current Status of the Initial Paradigm Shifter

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ABSTRACT

The concept of stereotactic radiosurgery (SRS) was first described by Lars Leksell in 1951. It was proposed as a noninvasive alternative to open neurosurgical approaches to manage a variety of conditions. In the following decades, SRS emerged as a unique discipline involving a collegial partnership among neurosurgeons, radiation oncologists, and medical physicists. SRS relies on the precisely guided delivery of high-dose ionizing radiation to an intracranial target. The focused convergence of multiple beams yields a potent therapeutic effect on the target and a steep dose fall-off to surrounding structures, thereby minimizing the risk of collateral damage. SRS is typically administered in a single session but can be given in as many as five sessions or fractions. By providing an ablative effect noninvasively, SRS has altered the treatment paradigms for benign and malignant intracranial tumors, functional disorders, and vascular malformations. Literature on extensive intracranial radiosurgery has unequivocally demonstrated the favorable benefit-to-risk profile that SRS affords for appropriately selected patients. In a departure from conventional radiotherapeutic strategies, radiosurgical principles have recently been extended to extracranial indications such as lung, spine, and liver tumors. The paradigm shift resulting from radiosurgery continues to alter the landscape of related fields.

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INTRODUCTION

In the early era of neurosurgery, conventional microsurgical tools were insufficient for complex intracranial pathology. For certain patients, operative morbidity and/or mortality were high and the complete resection of an intracranial lesion was not always feasible. Harvey Cushing, the founder of modern-day neurosurgery, resorted to the radium bomb to treat early brain tumors.[1] Walter Dandy borrowed a ureteral endoscope from Howard Kelly, a colleague in gynecology, and its use ushered endoscopy to neurosurgery procedures.[2]

Paradigm shifts in medicine often arise when substantial limits of existing approaches and a need for significant improvement to meet a clinical need are recognized. Elements comprising a paradigm shift are usually drawn from other arenas and are combined in a way not previously conceived, so that the resulting approach is a radical departure from the field and seems strangely foreign, even though the individual elements themselves may not be so. Hence, initial resistance on the part of some is the norm and not the exception. However, over time, the approach is embraced for its virtues and its limitations are appropriately recognized.

Stereotactic radiosurgery (SRS) is a classic example of a paradigm-shifting approach. It was devised out of necessity and blended distinct fields of neurosurgery, radiation oncology, and medical physics. Although the concept of radiosurgery has been present for more than six decades, radiosurgery continues to be refined and expanded. Thus, the paradigm shift is not yet complete. Herein, we describe radiosurgery's origins and current practice and speculate its future direction.

HISTORY

The field of SRS developed in the last century. Clarke and Horsley developed the initial stereotactic system, but this system was used for research.[3] Spiegel and Weeks[4] were the first to apply the stereotactic method for neurosurgery clinically. This approach allowed intracranial structures to be localized by their spatial relationship to a Cartesian coordinate system related to a ring rigidly secured to the skull.

A prerequisite to Lars Leksell's development of radiosurgery was frame-based stereotactic neurosurgery. Leksell wanted to devise a method to destroy localized structures situated deep within the brain but to do so without the same degree of morbidity associated with the open neurosurgical procedures of that era. His resulting idea was to converge multiple beams of ionizing radiation at one defined

point. While an inconsequential dose is delivered along the path of each beam, the point where the beams intersect receives a dose proportional to the sum total of the individual beams and would have a potent effect on the target tissue. The delivery device would be designed to ensure sharp fall off of delivered radiation at the edge of the intersection point. This would allow a precise effect at the targeted lesion and a minimized effect to the surrounding tissue. In 1951, Leksell defined this concept as stereotactic radiosurgery.[5]

Different types of ionizing radiation were tried. Leksell first used an orthovoltage x-ray tube coupled to a rigid stereotactic frame, which he used to treat several patients with trigeminal neuralgia or obsessive compulsive disorder.[5] Later, Leksell used a cyclotron as an accelerated proton source and treated various intracranial pathologies.[6,7] Rather than using the effects on the Bragg peak, they relied on the flat portion of the proton depth-dose profile that precedes the Bragg peak, called the plateau. Leksell named it "stralkiven," or ray knives.[8] The cyclotron, however, proved too cumbersome for intracranial radiosurgery, and a cyclotron's expense seemed to preclude its widespread application. Leksell and his team evaluated a first-generation linear accelerator for radiosurgery but, at that time, they found it to lack the inherent precision necessary for this approach. Stationary sources of high-energy photons emitting 60-Cobalt on to a fixed stereotactic target met the requirements of precision and compactness that Leksell had in mind for an intracranial radiosurgery system. Leksell and physicist Larsson oversaw the building of the first Gamma Knife unit between 1965 and 1968.

Around the time Leksell was developing the Gamma Knife, Raymond Kjellberg and Jacob Fabrikant were conducting innovative work in the field of radiosurgery using heavy particles from cyclotrons. And in 1983, in a hospital in Buenos Aires, Argentina, Betti and Derechinsky developed the concept of a modified linear accelerator for SRS.[9,10] Their system relied on a 10-MV linear accelerator and used a chair for the patient that was based on the Talairach stereotactic frame.[11] Winston and Lutz in Boston, MA; Hartman and Sturm in Heidelberg, Germany; Barcia-Salorio in Valencia, Spain; Colombo in Vincenza, Italy; and Podgorsak in Canada came up with other innovative developments in linear accelerator–based SRS devices shortly thereafter.[9,10,12-15]

Using a single high dose of ionizing beams to treat intracranial disorders was a novel and creative concept. Its application changed the direction of many fields such as neurosurgery and radiation oncology. Significant contributions have been made by numerous neurosurgeons, radiation oncologists, and physicists to advance the field of SRS. However, despite all the changes in SRS over the decades, the fundamental concepts have not changed.

THE DEFINITION, DEVICES, AND MULTIDISCIPLINARY APPROACH FOR SRS

Stereotactic radiosurgery was traditionally delivered in a single session, using specialized delivery devices. For the first couple of decades, SRS was delivered with regularity at only a handful of centers throughout the world. Over time, the successes of radiosurgery became evident to many. More clinicians were sufficiently trained and the technology became practical enough for diverse health systems to acquire. However, as the technology and indications evolved, the clinical volume of radiosurgery cases increased too. This in part prompted the need for a formal definition of radiosurgery. In March 2006, representatives of the American Association of Neurological Surgeons, Congress of Neurological Surgeons, and the American Society for Radiation Oncology met and formally defined radiosurgery.[16] Radiosurgery is the use of image-guided ionizing radiation to make inactive or eradicate a specific target within the brain or spine. Targeting is accomplished via high-resolution imaging and by using stereotactic principles. Radiosurgery is delivered through a rigid stereotactic guiding device, immobilization system, or image-guidance system. The ionizing radiation is delivered in one to five sessions. Although this definition is not universally sanctioned, the definition is the one most frequently applied for SRS.

From its inception, radiosurgery has been multidisciplinary. The definition sanctioned by the American Association of Neurological Surgeons, Congress of Neurological Surgeons, and the American Society for Radiation Oncology calls for the radiosurgery to be performed by a team consisting of a neurosurgeon, a radiation oncologist, and a medical physicist.[16] The American College of Radiology recommended a similar multidisciplinary approach to ensure quality of care and went so far as to specify responsibilities for the individual members of the multidisciplinary team during the SRS process.[17]

Radiosurgery can currently be delivered via a number of devices. Contemporary devices include the Gamma Knife Perfexion (Elekta AB, Stockholm, Sweden), Cyberknife (Accuray, Sunnyvale, CA), TrueBeam STx (Varian, Palo Alto, CA), and Novalis (Brainlab, Feldkirchen, Germany). Although it is more frequently used for fractionated radiation therapy, proton-beam systems at selected centers such as Massachusetts General Hospital (Boston, MA) are also used for radiosurgery.

CONTEMPORARY STEREOTACTIC RADIOSURGERY

Radiosurgery was the first method of dose escalation for late-responding tissues. Thus, radiosurgery has a preferred biologic effect on functioning pituitary adenomas, arteriovenous malformations, and some other intracranial malignancies. The radiobiologic effect of radiosurgery is partly because of a vascular effect and not purely a cytotoxic effect.[18]

SRS is currently performed on a diverse set of intracranial pathologies. Though a comprehensive review of all such practices goes beyond the scope of this article, we focus on three representative indications: pituitary adenomas, arteriovenous malformations, and brain metastases.

Stereotactic Radiosurgery for Pituitary Adenomas

SRS is used to treat a number of so-called benign intracranial tumors, and pituitary adenomas represent one such example. Pituitary adenomas are quite common among the general population; they comprise 10% to 20% of all intracranial tumors.[19,20] They are classified by size (microadenomas are < 1 cm in size; macroadenomas are ≥ 1 cm in size) and by hormonal secretory status (functioning lesions have hormone hypersecretion; nonfunctioning lesions have no abnormal hormone production).

In Table 1, we detail the major radiosurgical series of patients with nonfunctioning adenomas since 2002.[21-45] Single-session radiosurgery resulted in tumor-control rates of 83% to 100%, with a mean of 95.2%; new-onset hypopituitarism following radiosurgery was observed in 0% to 40% of patients, with a mean of 8.8% (Table 1).[21-45] At

Table 1. Major Radiosurgery Series for Nonfunctioning Pituitary Adenomas

Study	Publication Year	No. of Patients	Mean or Median Follow-Up (months)	Mean or Median Margin Dose (Gy)	Radiographic Tumor Control (%)
Feigl et al[19]	2002	61	55.2	15	94
Sheehan et al[28]	2002	42	31.2	16	97.6
Wowra et al[29]	2002	30	57.7	16	93.3
Petrovich et al[26]	2003	52	34	15	100
Losa et al[23]	2004	54	41.1	16.6	96.3
Muacevic et al[25]	2004	51	21.7	16.5	95
Kajiwara et al[22]	2005	14	32.1	12.6	92.9
Picozzi et al[27]	2005	51	40.6	16.5	96.1
Iwai et al[21]	2005	28	36.4	12.3	93
Mingione et al[24]	2006	100	46.4	18.5	92.2
Voges et al[41]	2006	37	56.6	13.4	100
Liscak et al[36]	2007	140	60	20	100
Pollock et al[38]	2008	62	64	16	96.8
Hoybye et al[20]	2009	23	78	20	100
Kobayashi et al[35]	2009	71	50.2	NR	96.7
Castro et al[30]	2010	14	42	12.5	100
Hayashi et al[33]	2010	43	36	18.2	100
Gopalan et al[32]	2011	48	95	18.4	83
Iwata et al[34]	2011	100	33	21 Gy/3 fr, 25 Gy/5 fr	98
Park et al[37]	2011	125	62	13	90
El-Shehaby et al[31]	2012	21	44	12	85
Runge et al[39]	2012	65	83	13	98.3
Starke et al[40]	2012	140	50.4	18	90
Wilson et al[42]	2012	51	50	14	100
Sheehan et al[43]	2013	512	36	16	93

Abbreviations: fr, fraction; NR, not reported.

the University of Virginia, we studied 140 patients with nonfunctioning pituitary adenomas, and we previously reported an approximately 90% tumor control and delayed hypopituitarism in 30% of patients.[42] New or worsening cranial nerve deficits were observed in 14% of patients. In a recent multicenter trial evaluating SRS for 512 patients with nonfunctioning pituitary adenomas (median follow-up, 36 months; range, 1 to 223 months), an overall tumor-control rate of 93% was reported.[45] SRS-related hypopituitarism was observed in 21% of patients.[45] Patients older than 50 years, those with tumor volumes less than 5 cm^3, and those without prior radiation therapy had more favorable outcomes of tumor control and neurologic preservation.[45]

The primary radiosurgical goal for functioning adenomas, unlike other benign intracranial tumors, is both endocrine remission and radiologic control. Radiologic control usually accompanies endocrine remission, but some adenomas exhibit radiologic control yet fail to achieve complete endocrine remission. Radiosurgery plays an important role in the treatment of persistent Cushing's disease and acromegaly refractory to surgical and/or medical management. Table 2 lists recent major radiosurgical series for Cushing's disease.[21,22,24,28,35,37,43,46-64] Endocrine remission was typically defined as a normal 24-hour urinary-free cortisol or serum cortisol. Most radiosurgical series for Cushing's disease show endocrine remission in the majority of patients after radiosurgery; the mean remission rate across major series is 51% (Table 2). The mean time interval after radiosurgery to endocrine remission in successfully treated patients is 12 months.[57] The most likely explanation for this finding is that radiosurgical doses typically required to attain endocrine remission in Cushing's disease are higher than those used to control the growth of nonfunctioning adenomas. Delayed endocrine recurrence after radiosurgery-induced remission can occur. For example, in a radiosurgical series of 90 patients with Cushing's disease, after a mean follow-up period of 45 months, Cushing's disease recurred in 10 patients at a mean time of 27 months after initial remission.[57]

For acromegaly, Table 3 lists recent major radiosurgical series.[21,24,28,35,40,43,46,47,50,52-54,60-63,65-84] Endocrine remission varied widely across series (range, 0% to 82%), but the mean remission rate for acromegalic patients after radiosurgery was 44.7%. Patients with a functioning adenoma volume of less than 3 cm^3 at the time of radiosurgery have been noted to have a significantly higher chance of endocrine remission.[62] Thus, a strong case can be made for maximum safe surgical resection before radiosurgery to increase the chance of endocrine remission. At the University of Virginia, the mean time to endocrine remission after radiosurgery for patients with acromegaly was 24 months, and this was longer than for comparable patients with Cushing's disease.[62] Although the data are drawn from retrospective studies, there seems to be compelling evidence to temporarily halt pituitary suppressive medications for patients with acromegaly around the time of radiosurgery; this approach seems to result in a greater rate of endocrine remission after SRS.[85]

Stereotactic Radiosurgery for Arteriovenous Malformations

After Roentgen discovered x-rays, there was substantial interest in using ionizing radiation to treat arteriovenous malformations

Table 2. Major Radiosurgical Series for Cushing's Disease

Study	Publication Year	No. of Patients	Mean or Median Follow-Up (months)	Mean or Median Margin Dose (Gy)	Endocrine Remission (%)
Izawa et al[45]	2000	12	26.4	23.8	16.7
Sheehan et al[49]	2000	43	39.1	20	63
Shin et al[50]	2000	6	88.2	32.3	50
Hoybye et al[22]	2001	18	16.8	NR	44
Feigl et al[19]	2002	4	55.2	15	60
Kobayashi et al[46]	2002	20	64	28.7	23.3
Laws et al[47]	2002	40	NR	20	74
Pollock et al[48]	2002	9	42.4	20	78
Choi et al[44]	2003	7	42.5	28.5	55.6
Petrovich et al[26]	2003	4	34	15	NR
Witt et al[52]	2003	8	24	24	0
Wong et al[53]	2003	5	38	NR	100
Devin et al[54]	2004	35	42	14.7	49
Kajiwara et al[22]	2005	2	38.5	26	50
Voges et al[41]	2006	17	58.7	16.4	52.9
Castinetti et al[76]	2007	40	54.7	29.5	42.5
Jagannathan et al[55]	2007	90	45	23	54
Petit et al[56]	2008	33	62	20	52
Pollock et al[57]	2008	8	73	20	87
Tinnel et al[58]	2008	12	37	25	50
Castinetti et al[51]	2009	18	94	28	50
Kobayashi et al[35]	2009	30	64.1	28.7	35
Wan et al[61]	2009	68	67.3	23	27.9
Hayashi et al[33]	2010	13	36	25.2	38
Sheehan et al[60]	2011	82	31	24	54
Wein et al[62]	2012	17	23	18	58.8
Grant et al[59]	2013	15	40.2	35	73

Abbreviation: NR, not reported.

(AVMs) and other vascular malformations (eg, aneurysms) through the period up to the mid-20th century. A long-term angiographic follow-up, albeit in a small series of AVMs treated with fractionated radiation therapy by Johnson in the 1950s,[86] revealed that 45% of AVMs were obliterated. However, other series treating AVMs with radiation had discouraging results, and therefore radiotherapy was often considered ineffective and was used as a last resort.[87,88]

With the introduction of Leksell's Gamma Knife, the therapeutic value of ionizing radiation for vascular malformations was re-evaluated. In Apri1 1970, the first radiosurgical treatment for an AVM was performed by Steiner et al[89] at the Karolinska Institute. Through a combination of intelligence and serendipity plus a bit of audacity, Steiner and his colleagues chose to deliver a near optimal radiosurgical dose of 25 Gy to the fistulous point of a sizeable AVM, and the AVM obliterated shortly thereafter. Unlike some other radiosurgical indications, AVM obliteration seems best accomplished using a single session (rather than multisession radiosurgery) and a generally high-margin dose (eg, 18 to 25 Gy). In an institutional series of 1,012 AVM patients treated with SRS at the University of Virginia, an overall obliteration rate of 69% was achieved; permanent deficits from SRS were observed in 2.2% of patients. Factors that led to the favorable outcome included no prior hemorrhage, AVM in a noneloquent location, and AVMs with a volume of less than 4 cm^3.[90] In another large series at the University of Pittsburgh, 906 patients with AVMs underwent radiosurgery and were eligible for 3 years of follow-up. Complete nidus obliteration was achieved in 78% of patients.[91] Adverse radiation effects occurred in 2.6% of patients. Major SRS series for AVMs are listed in Table 4.[91-98]

Embolization has been used to reduce an AVM nidus to a volume more suitable for radiosurgery. It is also frequently used to occlude arteriovenous fistulae, which are considered relatively radioresistant, and perinidal aneurysm, which is an accompanying vascular feature that is highly prone to rupture. Although a prospective study has not been undertaken, retrospective studies evaluating the effect of embolization before radiosurgery have generally demonstrated a reduction in obliteration compared with equivalent AVMs without prior embolization.

Stereotactic Radiosurgery for Brain Metastases

Though radiosurgery was used on AVMs and pituitary adenomas before malignant tumors, brain metastases have come to represent the single largest indication for SRS. The treatment of brain metastases historically has included whole-brain radiation therapy (WBRT), a therapeutic approach first reported in early 1950s.[99,100] The Radiation Therapy Oncology Group (RTOG) conducted numerous trials from 1971 to 1993 to investigate various doses and fractionation schemes for WBRT.[101-106] However, though neurologic symptoms and signs improved in the majority of patients, local control rates were low and neurologic death still occurred in 25% to 54% of patients with brain metastases.[101] Radiosurgery has come to represent an important approach for patients with brain metastases, either as a stand-alone treatment or used in conjunction with WBRT or resection.[107-113] Radiosurgery has been shown to offer a high rate of

Table 3. Major Radiosurgical Series for Acromegaly

Study	Publication Year	No. of Patients	Mean or Median Follow-Up (months)	Mean or Median Margin Dose (Gy)	Endocrine Remission (%)
Izawa et al[45]	2000	29	26.4	23.8	41.4
Shin et al[50]	2000	6	42.7	34.4	66.7
Zhang et al[79]	2000	68	34	31.3	36.8
Fukuoka et al[80]	2001	9	42	20	50
Ikeda et al[81]	2001	17	55.8	25	82
Feigl et al[19]	2002	9	55.2	15	60
Pollock et al[48]	2002	26	42.4	20	42
Attanasio et al[69]	2003	30	46	20	23
Choi et al[44]	2003	9	42.5	28.5	50
Muramatsu et al[78]	2003	4	30	27.5	50
Petrovich et al[26]	2003	5	34	15	NR
Witt et al[52]	2003	4	24	24	25
Castinetti et al[51]	2005	82	49.5	25	17
Gutt et al[77]	2005	44	22.8	18	47.7
Kajiwara et al[22]	2005	2	53.5	13.5	0
Koybayashi et al[75]	2005	67	63.3	18.9	4.8
Jezkova et al[71]	2006	96	53.7	35	50
Voges et al[41]	2006	64	54.3	16.5	37.5
Pollock et al[72]	2007	46	63	20	50
Roberts et al[73]	2007	9	25.4	21	44.4
Vik-Mo et al[74]	2007	61	66	26.5	17
Jagannathan et al[70]	2008	95	57	22	53
Losa et al[68]	2008	83	69	21.5	60.2
Pollock et al[57]	2008	27	46.9	20	67
Tinnel et al[58]	2008	9	35	25	44.4
Castinetti et al[76]	2009	43	102	24	42
Ronchi et al[69]	2009	35	120	20	46.0
Wan et al[61]	2009	103	67.3	21.4	36.9
Hayashi et al[33]	2010	25	36	25.2	40.0
Iwai et al[67]	2010	26	84	20	38.0
Poon et al[66]	2010	40	73.8	20-35	75
Sheehan et al[60]	2011	130	31	24	53
Franzin et al[65]	2012	103	71	22.5	60.7
Liu et al[64]	2012	40	72	21	47.5
Grant et al[59]	2013	13	40.2	35	61

Abbreviation: NR, not reported.

local tumor control and a low risk of adverse effects, including neurocognitive decline (Table 5; Fig 1).[109,110,114]

SRS WITH WBRT

Since the 1990s, trials investigated the use of SRS with WBRT in recurrent or newly diagnosed brain metastases, working under the hypothesis that the combination would better control brain metastases locally. Sanghavi et al[109] analyzed the outcome of 502 patients with brain metastases who were treated by SRS with WBRT in a large retrospective study from 10 institutions. Patients' median survival rate was 10.7 months, with favorable factors of higher Karnofsky performance score and lower recursive partitioning analysis (RPA) class. Adding SRS improved patients' median survival rates (16, 10, and 9 months for RPA classes 1, 2, and 3, respectively) versus rates for comparable patients who received WBRT alone (7, 4, and 2 months for RPA classes 1, 2, and 3, respectively).

RTOG 9508 is a level 1 study of patients with brain metastases treated with SRS plus WBRT versus WBRT alone.[114] This randomized clinical trial comprised 333 patients from 55 participating RTOG institutions. Patients had one to three newly diagnosed brain metastases on magnetic resonance image; each metastasis was ≤ 4 cm in diameter. Univariate analysis showed a survival advantage in the WBRT plus SRS group for patients with a single brain metastasis (median survival, 6.5 months *v* 4.9 months; $P = .04$). Patients in the SRS plus WBRT group were also more likely to have a stable or improved Karnofsky performance score at their 6 months' follow-up

Table 4. Major Radiosurgical Series for Arteriovenous Malformations

Study	Publication Year	No. of Patients	Obliteration Rate (%)	Complication Rate (%)
Lunsford[90]	1991	227	80	4.4
Steiner[94]	1992	247	81	4
Friedman[88]	2003	268	53	11
Shin[93]	2004	408	88	6.8
Maruyama[92]	2005	500	91	7.2
Liscak[89]	2007	330	92	3.4
Lunsford[91]	2008	906	78	2.6
Yen[95]	2013	1,023	68	1.8

Table 5. Significant Series Evaluating Radiation Therapy and Radiosurgery for Brain Metastasis

Study and Design	No. of Patients	No. of Lesions	Margin Dose (Gy)	Local Tumor Control at 1 Year (%)	Recurrence at 1 Year (%)	Median Overall Survival (months)
Patchell, 1990[114]						
WBRT	23	1	NA	48	NA	3.75
OP + WBRT	25	1	NA	80	NA	10.0
Noordijk, 1994[113]						
WBRT	63*	1	40 Gy/wk	NA	NA	6
OP + WBRT		1	40 Gy/wk	NA	NA	10
Auchter, 1996[107]						
SRS + WBRT	122	1	10-27 Gy (SRS) + 25-40 Gy (WBRT)	86	NA	14
Sanghavi, 2001[106]						
WBRT	502	NA	12-58 Gy	NA	NA	16.1
WBRT + SRS			12-58 Gy + NA	NA	NA	7.1
Sneed, 2002[103]						
SRS	268	Nolimit	NA	NA	NA	8.2 (RPA1), 8.6 (RPA2)
SRS + WBRT	301		NA + 30-50.4 Gy	NA	NA	14.0 (RPA1), 15.2 (RPA2)
Andrew, 2004[111]						
WBRT	164	1-3	37.5 Gy/3 wk	71	30	6.5
WBRT + SRS	167	1-3	37.5 Gy/3 wk + 15-24 Gy	82	25	4.9
Shehata, 2004[108]						
SRS	228	NA	7-30 Gy	87 (7 m FU)	NA	NA
SRS + WBRT	240		7-30 Gy + 6.75-50.4 Gy	97 (7 m FU)	NA	NA
Aoyama, 2006[120]						
SRS	67	1-4	18-25 Gy	72.5	76.4	8
SRS + WBRT	65	1-4	18-25 Gy + 30 Gy	88.7	46.8	7.5
Muacevic, 2008[110]						
OP + WBRT	33	1	40 Gy/4 wk	82	NA	9.5
SRS	31	1	14-27 Gy	96.8	NA	10.3
Chang, 2009[121]						
SRS	30	1-3	15-20 Gy	67	27	15.2
SRS + WBRT	28	1-3	15-20 Gy + 30 Gy/12 fr	100	73	5.7
Serizawa, 2010[123]						
SRS	778	1-10	13.5-30 Gy	98.4 (tiny) to 92.3 (small) to 77.9 (medium)	45.7	26.4 (RPA1), 8.4 (RPA2), 3.6 (RPA3)
Kocher, 2011[109]						
SRS + WBRT	99	1-3	20 Gy (SRS)	81	48	10.9 (WBRT)
SRS alone	100	1-3	30 Gy/10 fr (WBRT)	69	33	10.7 (no WBRT)
OP + WBRT	81	1-3		73	42	
OP alone	79	1-3		41	23	
Lal, 2012[122]						
SRS alone	31	1-3	15-20 Gy	NA	71	15.2
SRS + WBRT	27	1-3	15-20 Gy + 30 Gy/12 fr	NA	15	5.7
Yamamoto, 2013[124]						
SRS	548	1-4	10-32 Gy	91.5†	30.3†	7.9
SRS	548	> 5		96.1†	29.0†	7.0

Abbreviations: fr, fraction; FU, follow-up; GH, growth hormone; m, month; NA, not available; OP, operation; RPA, recursive partitioning analysis; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy; wk, weeks.
*Total No. of patients in this series.
†FU period was not mentioned.

than were patients assigned to WBRT alone (43% *v* 27%; $P = .03$). The risk of developing a local recurrence was 43% greater in the WBRT-alone group ($P = .002$). According to these results, Andrews et al[114] concluded that WBRT and SRS boost treatment improved functional status for all patients and survival rates for patients with a single unresectable brain metastatic lesion.

Aoyama et al[115] also conducted a randomized trial of SRS versus SRS plus WBRT (Japanese Radiation Oncology Study Group trial 99-1). They attempted to determine whether WBRT combined with SRS versus SRS alone improved survival, brain tumor control, functional preservation rate, and frequency of neurologic death. Between 1999 and 2003, they enrolled 132 patients who had one to four brain metastases (each less than 3 cm in diameter) onto the study and randomly assigned the patients to receive SRS alone versus SRS plus WBRT. The median survival time and the 1-year actuarial survival rates were 7.5 months and 38.5% in the WBRT plus SRS group and 8.0

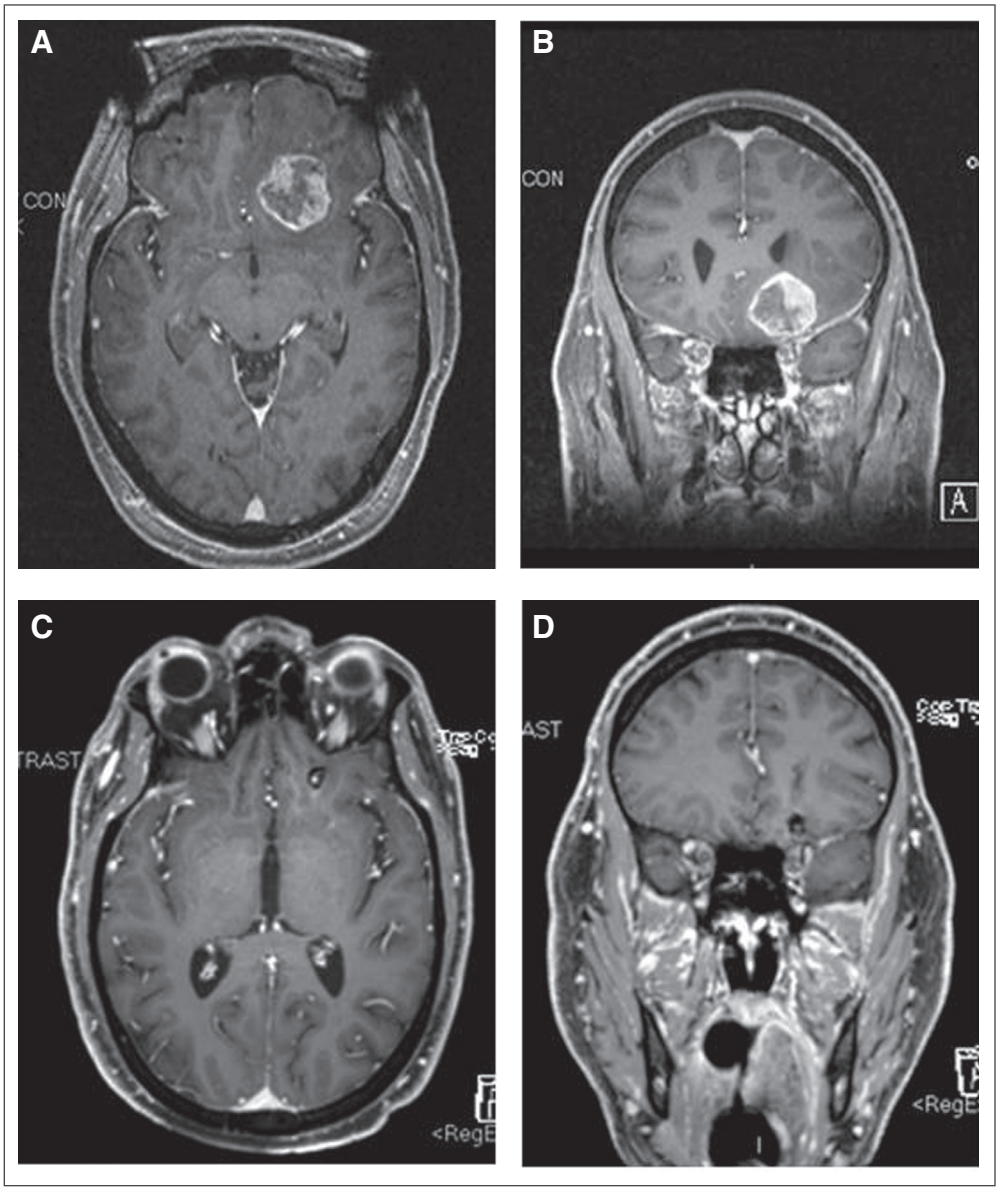

Fig 1. (A) T1 axial and (B) coronal T1 postcontrast magnetic resonance image (MRI) of a patient with a left inferior frontal brain metastasis obtained at the time of stereotactic radiosurgery. (C and D) The comparable follow-up MRIs of the brain 20 months later show substantial tumor regression.

months and 28.5% for SRS alone ($P = .42$). Aoyama et al[115] concluded that the use of WBRT plus SRS versus SRS alone did not improve survival rates for patients with one to four brain metastases, but intracranial relapse occurred considerably more frequently in those patients who did not receive WBRT. In their follow-up article, Aoyama et al[116] also mentioned that the most important factor to influence stabilization of neurocognitive function was brain tumor control.

In a study by Chang et al,[117] patients with one to three brain metastases were randomly assigned to SRS plus WBRT or SRS alone. The trial was stopped by the data monitoring committee secondary to an increased probability of neurocognitive decline in the patients treated with WBRT. This decline was observed in learning and memory function indices 4 months after treatment. An accompanying cost-effectiveness analysis demonstrated a higher effectiveness for SRS and observation in patients with one to three brain metastases.[118]

In a trial by the European Organisation for Research and Treatment of Cancer, Kocher et al[112] demonstrated the other view of adjuvant WBRT after SRS; 359 patients with one to three brain metastases were treated with complete surgery or radiosurgery and were then randomly assigned to adjuvant WBRT (30 Gy in 10 fractions) or observation. Kocher et al set the primary end point as time to WHO performance status deterioration to more than 2. They found that the median time to WHO performance status of more than 2 was 10.0 months after observation and 9.5 months after WBRT. Overall survival was similar in the WBRT and observation arms. However, WBRT reduced the 2-year relapse rate both at the initial sites and new sites, and salvage therapies were used more frequently after observation than after WBRT. They concluded that adjuvant WBRT reduced intracranial relapses and neurologic deaths but failed to improve the duration of functional independence and overall survival.

Tsao et al[119] summarized these randomized clinical trials (RCTs) in 2013. In their meta-analysis report, two RCTs reported on the WBRT and SRS boost versus WBRT alone in patients with two to four brain metastases and found no difference in overall

survival, but local tumor control was significantly favored by the WBRT plus SRS boost. Three RCTs reported on SRS alone versus the WBRT plus SRS boost for patients with one to four brain metastases and found there was no difference in overall survival, but local tumor control was also significantly favored in the WBRT plus SRS boost group. Conclusively, for a limited number of brain metastases, there are no survival benefits for WBRT plus SRS boost compared with SRS alone. Although additional WBRT improves local and distant brain metastases control, SRS alone should be considered a routine treatment owing to better neurocognitive outcomes and a lower risk of late adverse effects.

SRS AS A SOLE TREATMENT APPROACH

For radioresistant histologies such as melanoma, SRS alone has long been a popular approach. Treating radioresistant histologies with WBRT has disadvantages[120] and adverse effects, particularly in terms of neurocognition, that make WBRT less appealing to selected patients and their treating physicians. Nevertheless, when considering the adverse effects on quality of life and neurologic function of long-term survivors,[116,117] the use of SRS alone is becoming more and more popular. Regarding tumor control, the rationale against using WBRT with SRS is that the benefit of WBRT on nonvisualized brain metastases is mitigated by the fact that once WBRT ends, any new metastases are now untreated. Hence, recurrent brain metastases are best treated expectantly by delayed WBRT or repeat SRS.

Sneed et al[106] collected clinical data from 10 institutions and compared the survival rates of patients with newly diagnosed brain metastases. For all RPA classes, the median survival times for patients were comparable between the two treatment groups (RPA class I, 14 months *v* 15 months; RPA class 2, 8 months *v* 7 months; RPA class III, 5 months *v* 6 months). The report concluded that the upfront WBRT did not improve survival compared with SRS alone.

The Japanese Leksell Gamma Knife Society undertook a prospective study (JLGK 0901 study) of SRS without WBRT to establish evidence that such a treatment strategy is feasible for five to 10 brain metastases. A preliminary report showed that the overall survival rate for patients with five to 10 brain metastases was almost the same as that of patients with two to four brain lesions.[121] More recently, Yamamoto et al[122] demonstrated a post-SRS median survival difference of 0.9 months between the two groups, suggesting noninferiority when using SRS alone for patients with five or more brain metastases.

The role of radiosurgery for brain metastasis has expanded significantly over the past decade. It can be used as either an upfront treatment or after prior WBRT. Radiosurgery affords a high rate of local tumor control, even in radioresistant histologies. Although radiosurgery seems to avoid collateral damage that can translate to neurocognitive decline, it does so at the risk of greater distant intracranial disease progression over time and may require salvage treatment such as repeat SRS, WBRT, or resection.

FUTURE DIRECTIONS FOR STEREOTACTIC RADIOSURGERY

Radiosurgery has shown substantial growth. Beginning in 2003 in the United States, SRS was more frequently performed than craniotomy for nonmeningioma tumors.[123] There has also been a dramatic increase in access to radiosurgical services throughout much of the world, and a premium is being placed on radiosurgical education and training.[123,124] It is clear that radiosurgery has altered practice patterns and will have a lasting presence in the treatment of patients with intracranial disorders.

Radiosurgery indications are also likely to expand. An initial multicenter prospective trial examining the use stereotactic radiosurgery for mesial temporal lobe epilepsy was completed and showed reasonable success.[125] This prompted funding for the Radiosurgery or Open Surgery for Epilepsy trial by the National Institutes for Health. Radiosurgery for functional and psychiatric indications have also shown renewed interest as of late.[126,127]

Traditional radiosurgery was delivered in a single session. However, with the advent of relocatable immobilization systems and reliable intrafraction image guidance systems, multisession radiosurgery has also led to broader indications for this discipline.[128,129] A multisession approach capitalizes on the four R's of radiation therapy and the greater ease of radiosurgical delivery even when the target abuts a radiation-sensitive critical structure.[130]

The principles of radiosurgery have also extended to extracranial sites. In 1996, Hamilton et al[131] reported on radiosurgery for spinal lesions. Since then, spinal radiosurgery has been added to the treatment armamentarium for patients with metastases, arteriovenous malformations, and benign spinal tumors such as neurofibromas.[132-134] This and other extracranial applications in the burgeoning field of stereotactic body radiation therapy are discussed in more detail in other articles in this issue.

CONCLUSION

In the more than six decades since its conception, stereotactic radiosurgery has disrupted old approaches and led to improved treatment of patients with intracranial disorders. The principles of Leksell have stood the test of time and continue to shape the fields of neurosurgery and radiation oncology. The ripples of radiosurgery are even being felt beyond the traditional intracranial realm and are affecting the management of patients with spinal and thoracic pathologies. Technologic refinements, appropriate education and training, and preserving the multidisciplinary approach for SRS will likely lead to further benefits for patients and further growth for the field.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Final approval of manuscript: All authors

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