Clinical Outcomes of Stereotactic Radiosurgery in the Treatment of Patients with Metastatic Brain Tumors

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Key words
- Brain metastases
- Stereotactic radiosurgery
- Surgery
- Survival
- Tumor control
- Whole-brain radiation therapy

Abbreviations and Acronyms
CNS: Central nervous system
GK: Gamma knife
KPS: Karnofsky Performance Score
LINAC: Linear accelerator
NSCLC: Non–small-cell lung cancer
RPA: Recursive partitioning analysis
RTOG: Radiation Therapy Oncology Group
SCLC: Small-cell lung cancer
SRS: Stereotactic radiosurgery
WBRT: Whole-brain radiation therapy

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BACKGROUND: **Stereotactic radiosurgery (SRS) is a form of radiation therapy that delivers a focused, highly conformal dose of radiation to a single volume, while minimizing damage to the adjacent nervous tissue. The efficacy of SRS has been examined in the treatment of patients diagnosed with brain metastases due to the fact that it is capable of targeting any region in the brain and can irradiate multiple tumors in the same treatment setting in a noninvasive fashion.**

METHODS: **Modern literature was reviewed for studies on SRS in the treatment of patients with brain metastases.**

RESULTS: **After assessing patient age, Karnofsky Performance Score (KPS), control of primary cancer, presence of extracranial metastases, number of brain metastases, location of brain metastases, and size of brain metastases, SRS offers suitable patients a viable, less invasive treatment option. In patients with 1 to 4 brain metastases who have a KPS ≥70, the addition of SRS to whole-brain radiation therapy (WBRT) produces increased levels of survival and local tumor control when compared with patients treated with WBRT alone. The available evidence suggests that specific patients treated with SRS alone exhibit superior levels of survival and tumor control when compared with patients treated with WBRT alone. Further evidence in the form of a randomized trial is needed to confirm this observation. Questions remain regarding survival and tumor control in patient groups treated with SRS with or without WBRT. Recently published randomized evidence reported a survival advantage in patients treated with SRS alone. These data differ from other previously published randomized evidence, as well as several prospective and retrospective studies, which reported nonsignificant survival differences. Contrasting evidence also exists pertaining to local and distant tumor control, which warrants further investigation into this matter. The available evidence suggests that in patients with 1 to 2 brain metastases, both SRS alone and SRS with WBRT offer equivalent levels of survival when compared with patients treated with surgery with WBRT. Research has been conducted that reports a survival advantage in patients with 1 to 3 brain metastases that were treated with SRS with WBRT.**

CONCLUSIONS: **SRS can be an advantageous course of treatment in specific patient groups when utilized alone, after surgery, with WBRT, or in combination with either or both of the treatment modalities. Although treatment approaches have been refined, many questions remain unanswered and further clinical evidence is needed to guide physicians in their future treatment decisions regarding treating patients in specific clinical scenarios.**

INTRODUCTION

As advances in imaging technologies and the treatment of extracranial disease allow the longevity of cancer patients to increase, the incidence of brain metastases has grown (occurring in up to 40% of cancer cases) (12). Regions of the brain that receive a larger blood supply are more at risk in developing one or more metastatic brain tumors than other areas of the brain (7). As a consequence, 80% of brain metastases are hemispheric, whereas 15% arise within the cerebellum and 5% arise within the brain stem. Cancers originating from the lung are responsible for approximately 30% to 60% of brain metastases (40). However, metastasis to the brain originating from melanoma, breast cancer, colorectal cancer, renal cell carcinoma, and carcinoma of multiple other origins are also frequently observed (40).

Patients who suffer from brain metastases have a poor prognosis and are estimated to survive 1 to 2 months when treated solely with corticosteroids (1). Whole-brain radiation therapy (WBRT) is considered to be a

Table 1. Randomized Trials of WBRT with or Without Surgery in the Treatment of Patients with a Single Brain Metastasis

Author	Patients in Treatment Arms	Median Survival Time	Median Time of Functional Independence	Patients with Local Tumor Recurrence
Patchell et al., 1990 (26)	WBRT: $n = 23$	WBRT: 15 weeks	WBRT: 8 weeks	WBRT: 12
	WBRT/surgery: $n = 25$	WBRT/surgery: 40 weeks ($P < 0.01$)	WBRT/surgery: 38 weeks ($P < 0.005$)	WBRT/surgery: 5 ($P < 0.02$)
Vecht et al., 1993 (42)	WBRT: $n = 31$	WBRT: 6 months	WBRT: 15 weeks	NR
	WBRT/surgery: $n = 32$	WBRT/surgery: 10 months ($P = 0.04$)	WBRT/surgery: 33 weeks ($P = 0.06$)	
Mintz et al., 1996 (22)	WBRT: $n = 43$	WBRT: 6.3 months	WBRT: 9 weeks	NR
	WBRT/surgery: $n = 41$	WBRT/surgery: 5.6 months ($P =$ NS)	WBRT/surgery: 8 weeks ($P =$ NS)	

NR, not reported; NS, nonsignificant; WBRT, whole-brain radiation therapy.

mainstay of treatment for approximately 70% to 80% of patients diagnosed with brain metastases (14, 27). WBRT is capable of eliminating rapidly dividing tumor cells in all regions of the brain. Because of the differential susceptibility to radiation therapy between tumor cells and nervous tissue, WBRT is one effective treatment modality that can extend the patient's life an average of 4 to 7 months with no surgical or radiosurgical treatment (12, 40). Studies have demonstrated that surgical resection followed by WBRT provides patients with a single, surgically accessible brain metastasis a better prognosis when compared with patient groups treated with WBRT alone or surgical resection alone (25, 26, 42). However, many physicians believe neurosurgical intervention for patients with multiple metastatic tumors is a drastic and potentially harmful course of treatment (35).

Stereotactic radiosurgery (SRS) is a form of radiation therapy that is capable of delivering a highly conformal dose of radiation to a target specified by computer planning in a single treatment. The patient's skull is immobilized, allowing a high dose of radiation to be delivered to the tumor volume with precision, while sparing the adjacent nervous tissue. Unlike the traditional neurosurgical modalities, SRS is a noninvasive treatment regimen that has the ability to precisely target any region in the brain and can irradiate multiple lesions in the same treatment setting. Due to those advantages, the role of SRS in the treatment of patients with brain metastases is continuously increasing. Recently, Linskey et al. (20) published a clinical practice guideline on the role of SRS in the management of patients with newly diagnosed brain metastases in an evidence-based fashion from 1990 to 2008. The authors addressed the need of WBRT in patients where SRS is prescribed and the role of WBRT when SRS is delivered after surgical resection, as well as comparing single-dose SRS with multidose SRS.

The goal of this article is to provide a modern review of the literature thoroughly analyzing the efficacy of SRS alone or in a multimodality management approach compared with the traditional courses of treatment for patients who present with single or multiple metastatic brain tumors. In addition, this article also discusses the specific treatment planning and patient results associated with SRS, as well as evaluating the randomized controlled trials analyzing patients treated with WBRT with or without surgical resection and patients treated with surgical resection with or without WBRT to ultimately show the extent in which SRS has evolved in the treatment of patients with brain metastases.

REVIEW AND COMPARISON OF TREATMENT MODALITIES

Literature Search Strategy

To identify contemporary comparative studies assessing the clinical outcomes of patients treated with SRS for brain metastases, a PubMed search from 2000 to June 2010 was performed. Keywords for search included "stereotactic radiosurgery OR radiosurgery brain metastases OR brain metastasis." Comparative studies analyzed in this review included randomized controlled trials, prospective cohort studies, and retrospective cohort studies with ≥8 evaluated patients. Studies published only in abstract form and studies assessing patients treated with multidose SRS were excluded. Due to our broad search strategy and the vast amount of world literature, references from existing review articles were also selected and analyzed for study inclusion eligibility. In addition, randomized controlled trials assessing patients treated with WBRT with or without surgical resection and patients treated with surgical resection with or without WBRT published from 1990 to June 2010 were included in this review to ultimately show the evolving nature of SRS in the treatment of patients with metastatic brain disease and were identified based on citations in existing review articles found from our initial PubMed search.

WBRT with or Without Surgery

Because neurosurgical tumor resection for patients with multiple brain tumors is considered to be an excessive course of treatment, surgery combined with WBRT is only recommended for patients with a single, surgically accessible brain metastasis or for patients who have a dominant metastasis causing focal neurological symptoms due to intracranial pressure or mass effect. Three randomized trials have been conducted evaluating the efficacy of surgical resection followed by WBRT compared with WBRT alone for patients with a single brain metastasis (**Table 1**). The first was published in 1990 by Patchell et al. (26). A total of 48 patients with a single brain metastasis were randomly assigned to a surgical resection followed by postoperative WBRT

Table 2. WBRT with or Without SRS in the Treatment of Patients with Single or Multiple Brain Metastases

Author/Study Type	# BM	Study Endpoints	WBRT	WBRT/SRS	*P* Value
Andrews et al., 2004 (1)/ randomized	1–3	Overall MS	6.5 months	5.7 months	NS
		1 BM MS	4.9 months	6.5 months	0.0393
		1-year local control rate	71%	82%	0.01
		6-months KPS rate	27%	43%	0.03
Kondziolka et al., 1999 (16)/ randomized	2–4	MS	7.5 months	11 months	NS
		1-year local failure rate	100%	8%	0.0005
		Median local recurrence time	6 months	36 months	0.0016
Li et al., 2000 (19)/ prospective cohort	1	MS	5.7 months	10.6 months	<0.0001*
		Tumor response rate	48%	89%	0.004*
		Median local recurrence time	4 months	8.6 months	0.0000*
		Median distant recurrence time	4.1 months	8.6 months	0.0000*
Wang et al., 2002 (43)/ retrospective cohort	1–6	MS	37 weeks	91 weeks	<0.00001†
		1-month local tumor control rate	88%	96%	NR
Sanghavi et al., 2001 (34)/ retrospective cohort	BM	MS RPA class 1	7.1 months	16.1 months	<0.05
		MS RPA class 2	4.2 months	10.3 months	<0.05
		MS RPA class 3	2.3 months	8.7 months	<0.05

BM, brain metastases; KPS, Karnofsky Performance Score; MS, median survival; NR, not reported; NS, nonsignificant; RPA, recursive partitioning analysis; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
*Data include SRS-alone treatment arm.
†Data include SRS-alone and surgery-alone treatment arms.

group (25 patients) or a needle biopsy followed by WBRT group (23 patients). The total prescribed radiation dose for both groups was 36 Gy, which was delivered in 12 daily fractions of 3 Gy each. Patients who did not require urgent focal treatment for an acute neurological deficit, with a Karnofsky Performance Score (KPS) ≥70 were eligible for the study. It was reported that the surgical resection with WBRT group lived a statistically significant ($P < 0.01$) amount of time longer than the WBRT-alone group (median of 40 vs. 15 weeks). Patients in the surgical arm also experienced less frequent tumor recurrence ($P < 0.02$) at the original site of metastasis, along with a longer time of functional independence ($P < 0.005$) compared with the WBRT-alone arm (median of 38 vs. 8 weeks).

In 1993, Vecht et al. (42) published the second randomized trial analyzing WBRT with or without surgical resection. The authors randomized 63 evaluable patients with a single brain metastasis to a surgical resection with WBRT group and a WBRT-alone group. Patients were ineligible if they spent more than 50% of their day in bed. A total radiation dose of 40 Gy was delivered in 2 fractions per day of 2 Gy each. Similar to the results of Patchell et al. (26), it was found that the addition of surgery offered patients an increased period of survival ($P = 0.04$), living a median of 10 months, whereas the WBRT-alone group lived a median of 6 months. Functional independence reached near statistical significance ($P = 0.06$), favoring the surgical resection with WBRT arm.

The third and most recent randomized trial was conducted by Mintz et al. (22) in 1996. A total of 84 patients with a single cerebral metastasis, who were <80 years old and had a KPS of ≥50, participated in the study. Specifically, 41 patients were assigned to the surgical arm and 43 patients were assigned to the WBRT-alone arm. The total radiation schedule delivered was 30 Gy given in 10 daily fractions of 3 Gy each. In contrast to the 2 prior studies, it was reported that the surgical resection with WBRT group and the WBRT-alone group did not differ in terms of survival ($P = 0.24$), where the surgical arm survived a median of 5.6 months and the WBRT-alone arm survived a median of 6.3 months. This study, however, contained a greater number of patients with lower KPS values and progressive extracranial cancer, which could have resulted in a higher proportion of patients succumbing to their primary cancer before the effects of surgery could manifest (11).

WBRT with or Without Stereotactic Radiosurgery

After it was shown that surgical resection followed by WBRT provided patients with a single brain metastasis an improved longevity when compared with patient groups treated with WBRT alone, the outcomes of patient groups treated with SRS with WBRT were analyzed and compared with the traditional treatment modalities (**Table 2**). Patients with a single, surgically accessibly brain metastasis who have a severe neurologic deficit, a ventricular obstruction, a tumor ≥40 mm, or a significant mass effect often are treated with neurosurgery followed by WBRT (12). SRS has shown success in patients who have manageable neurological symptoms, a tumor/s diameter ≤30 mm, a surgically inaccessible brain metastasis, or multiple brain metastases.

Two randomized trials have been published evaluating the addition of SRS to WBRT. The most recent, which was conducted by the Radiation Therapy Oncology Group (RTOG), was published in 2004 (1). A total of 333 patients were randomized into an SRS with WBRT arm (167 patients) and a WBRT-alone arm (164 patients). Eligible patients possessed 1 to 3 brain metastases, a KPS ≥70, and a maximum tumor diameter of 40 mm for the largest lesion and a diameter of ≤30 mm for the remaining lesions. The author's main outcome was patient survival, whereas the other variables assessed were local tumor control, overall brain tumor control, KPS, and cause of death. There were no statistically significant differences in terms of survival between the 2 groups. However, patients who were treated with SRS with WBRT who possessed a single brain metastasis survived a median of 6.5 months, whereas the other patients survived a median of 4.9 months ($P = 0.0393$). In addition, patients with 1 to 3 brain metastases were likely to have an increased local control level ($P = 0.01$) at 1 year of follow-up and an increased KPS ($P = 0.03$) at 6 months of follow-up.

The other randomized trial of WBRT with or without SRS was performed by Kondziolka et al. (16) in 1999. Only 27 patients participated in the study, where 13 patients were randomized into the SRS with WBRT group and 14 patients were randomized into the WBRT-alone group. All patients had a KPS ≥70, 2 to 4 metastatic brain tumors, and tumor diameters ≤25 mm. In contrast to the RTOG study by Andrews et al. (1), the main outcome assessed was local tumor control. Other variables analyzed were median survival time and tumor recurrence at the original site. The authors stopped the study at the 60% accrual point because they witnessed a drastic difference in tumor control between the 2 treatment arms. Median survival favored the radiosurgery arm, but was not statistically significant because there was a relatively small number of patients in the study (11 vs. 7.5 months). It was also observed that the SRS with WBRT group had a better local failure rate at 1 year (8% vs. 100%) and median time of recurrence (36 vs. 6 months) when compared with the WBRT-alone group.

In addition, we evaluated 2 retrospective cohort studies (34, 43) and 1 prospective cohort study (19), all of which were published in the last 10 years. All studies reported a statistically significant increase in median survival in patient groups treated with SRS with WBRT compared with patient groups treated with WBRT alone. The 3-arm prospective study by Li et al. (19) limited patients suffering from non–small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) with a single brain metastasis ≤45 mm in diameter, whereas the 4-arm retrospective cohort study by Wang et al. (43) included patients with 1 to 6 brain metastases who had a KPS ≥40 and tumor/s < 40 mm in diameter. The other retrospective cohort study by Sanghavi et al. (34) evaluated 502 patients from databases of 10 institutions. Survival was more pronounced in patients with a higher KPS ($P = 0.0001$), a controlled primary cancer ($P = 0.0023$), the absence of extracranial cancer ($P = 0.0001$), and a lower recursive partitioning analysis (RPA) class ($P = 0.000007$). Whereas Li et al. (19) found that patients in the radiosurgery arm had an increased local tumor control rate ($P < 0.0001$) and median time of tumor recurrence ($P < 0.00001$), Wang et al. (43) found comparable 1-month local tumor control rates between the 2 treatment arms. However, because the data by Wang et al. (43) were collected at only 1 month after treatment, it is possible that the clinical outcomes observed with the addition of SRS to WBRT did not have enough time to manifest, which explains the nonsignificant difference in local control between the 2 treatment arms. Sanghavi et al. (34) did not report tumor control and recurrence data.

Surgery with or Without WBRT

Surgical resection followed by WBRT was proven to be a superior treatment modality when compared with WBRT alone; however, questions arose pertaining to the relevance of WBRT in the treatment regimen. The only randomized trial evaluating the efficacy of surgical resection followed by WBRT compared with surgical resection alone was performed by Patchell et al. (25) in 1998. A total of 95 patients were randomized into a surgical resection with WBRT arm and a surgical resection-alone arm. Specifically, 49 patients had WBRT in addition to surgery, whereas the other 46 patients did not. There was not a statistically significant difference in median survival and functional independence between the 2 treatment arms. It was reported, however, that the surgical resection followed by WBRT group showed less frequent tumor recurrence at the site of the original metastasis ($P < 0.001$), showed less frequent tumor recurrence anywhere in the brain ($P < 0.001$), and were less likely to die of neurological causes ($P = 0.003$) than the surgical resection-alone treatment arm.

Stereotactic Radiosurgery Plus WBRT Compared with Surgery Plus WBRT

Once SRS with WBRT and surgical resection with WBRT proved to be effective treatment modalities for patients with brain metastases, several studies were published comparing the 2 treatment therapies. No randomized trials have been published comparing SRS with WBRT to surgical resection with WBRT. We reviewed 4 retrospective cohort studies all published in the last 10 years (24, 30, 31, 36) (**Table 3**).

In 2009, Rades et al. (30) performed a matched-pair analysis evaluating a total of 94 patients with 1 or 2 brain metastases. Specifically, 47 patients were treated with SRS with WBRT and another 47 patients received surgical resection with WBRT. The authors reported that there was not a statistically significant difference between the 2 treatment arms in 1-year survival rates, 1-year intracerebral control rates, and 1-year local control rates. In the same year, Rades et al. (31) published another matched-pair analysis comparing the 2 treatment modalities in patients with 1 to 3 brain metastases. A total of 52 patients were placed in each treatment arm, respectively. In contrast to patients with 1 to 2 brain metastases, patients with 1 to 3 brain metastases who underwent SRS with WBRT showed a statistically significant increase in 1-year survival rates ($P = 0.034$), 1-year intracerebral control rates ($P = 0.003$), and 1-year local control rates ($P = 0.006$).

O'Neill et al. (24) evaluated a total of 97 patients with a single brain metastasis treated with either SRS with or without WBRT (23 patients) or surgical resection with or without WBRT (74 patients). One-year survival favored the surgery group (62% vs. 56%), but did not reach statistical significance ($P = 0.15$). Additionally, the authors observed that the 2 groups did not differ in terms of toxicity, neurological cause of death, and median time of tumor recurrence. This study could be criticized due to the large difference in the number of patients between the 2 treatment arms.

Table 3. SRS plus WBRT vs. Surgery plus WBRT in the Treatment of Patients with Single or Multiple Brain Metastases

Author/Study Type	# BM	Study Endpoints	SRS/WBRT	Surgery/WBRT	*P* Value
Rades et al., 2009 (30)/ retrospective cohort	1–2	1-year survival rate	65%	63%	NS
		1-year IC rate	70%	78%	NS
		1-year LC rate	84%	83%	NS
Rades et al., 2009 (31)/ retrospective cohort	1–3	1-year survival rate	56%	47%	0.034
		1-year IC rate	66%	50%	0.003
		1-year LC rate	82%	66%	0.006
O'Neill et al., 2003 (24)/ retrospective cohort	1	1-year survival rate	56%	62%	NS
		Local recurrence rate	0%	17%	NR
		Overall recurrence rate	29%	30%	NR
Schoggl et al., 2000 (36)/ retrospective cohort	1	MS	12 months	9 months	NS
		Local recurrence rate	5%	17%	NR
		Local recurrence time	4.9 months	3.9 months	<0.05
		Distant recurrence rate	10%	15%	NR
		Distant recurrence time	4.4 months	3.7 months	NS

BM, brain metastases; IC, intracerebral control; LC, local control; NR, not reported; NS, nonsignificant; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

Similarly, Schoggl et al. (36) conducted a study in which 133 patients with a single brain metastasis underwent SRS with WBRT (67 patients) or surgical resection with WBRT (66 patients). Median survival favored the SRS group (12 vs. 9 months), but did not reach statistical significance ($P = 0.19$). However, it was reported that patients in the SRS group showed an improved local control rate ($P < 0.05$) and a decreased neurological death rate (12.5% vs. 21.8%) when compared with the surgery group.

Stereotactic Radiosurgery Alone Compared with WBRT Alone

No randomized trials have been published comparing patient groups treated with SRS alone against those treated with WBRT alone. We reviewed a 3-arm prospective cohort study (19) and 6 retrospective cohort studies (6, 15, 18, 32, 33, 43), all of which were published in the last 10 years (**Table 4**). The 3-arm prospective cohort study by Li et al. (19) evaluated patient groups treated with SRS alone, WBRT alone, or SRS with WBRT. One of the retrospective cohort studies by Rades et al. (33) was a 4-arm study that evaluated elderly patients treated with SRS alone, WBRT alone, surgical resection with WBRT, or surgical resection plus WBRT plus SRS boost. The retrospective cohort study by Wang et al. (43) was also a 4-arm study that compared patients treated with SRS alone, WBRT alone, surgical resection alone, and SRS with WBRT.

The most recent of these studies was that of Rades et al. (33) in 2008. Patients ≥65 years of age who were diagnosed with 1 to 2 metastatic brain tumors were treated with WBRT alone (34 patients), SRS alone (43 patients), surgical resection with WBRT (41 patients), or surgical resection plus WBRT plus SRS boost (46 patients). The SRS-alone treatment arm had an increased 1-year survival rate (40%) when compared with the WBRT-alone treatment arm (17%). The 1-year intracerebral control rate (55% vs. 17%) and 1-year local control rate (68% vs. 19%) also favored the SRS-alone treatment group.

In 2007, Rades et al. (32) published a study analyzing the role of SRS in 186 patients with 1 to 3 brain metastases ≤40 mm in diameter, who were classified in either RPA class 1 or class 2. A total of 91 patients who received a WBRT dose of 30 to 40 Gy and 95 patients who received an SRS dose of 18 to 25 Gy were eligible candidates for the study. The authors reported that the SRS-alone group showed a statistically significant ($P = 0.045$) increase in median survival compared with the WBRT-alone group (13 vs. 7 months). In addition, the SRS-alone treatment arm had a substantially improved 1-year local and overall brain control rate when compared with the WBRT-alone treatment arm. These results correlate with those found by Kocher et al. (15) in 2004, who reported statistically significant increases in median survival in RPA class 1 ($P < 0.0001$) and RPA class 2 ($P < 0.04$) in 255 patients with 1 to 3 brain metastases. Patients in the 2 treatment arms classified in RPA class 3 did not show compelling differences in median survival. Increases in median survival in the SRS-alone group were also reported by Lee et al. (18) (29 vs. 6 months) and Wang et al. (43) (67 vs. 37 weeks).

All patients who participated in the 3-arm prospective cohort study by Li et al. (19) had a single brain metastasis ≤45 mm in diameter, a KPS ≥60, and either SCLC or NSCLC. A total of 23 patients were placed in the SRS-alone treatment arm, whereas 29 patients were placed in the WBRT-alone treatment arm. The authors reported that median survival was higher in the SRS-alone treatment group (9.3 vs. 5.7 months). Also, a greater proportion of patients showed either partial or complete tumor response in the SRS-alone arm compared with the WBRT-alone arm (87% vs. 48%).

Datta et al. (6) compared the overall survival rate in patients with brain metastases who were treated with gamma knife (GK) SRS with or without WBRT (22.6% of patients), or WBRT alone. Specifically, 53 patients were treated with GK radiosurgery

Table 4. SRS Alone vs. WBRT Alone in the Treatment of Patients with Single or Multiple Brain Metastases

Author/Study Type	# BM	Study Endpoints	SRS	WBRT	*P* Value
Rades et al., 2008 (33)/ retrospective cohort	1–2	1-year survival rate	40%	17%	0.043*
		1-year IC rate	55%	17%	<0.001*
		1-year LC rate	68%	19%	<0.001*
Rades et al., 2007 (32)/ retrospective cohort	1–3	MS	13 months	7 months	0.045
		1-year LC rate	64%	26%	<0.001
		1-year DC rate	61%	66%	NS
		1-year OC rate	49%	23%	0.005
Kocher et al., 2004 (15)/ retrospective cohort	1–3	MS: RPA class 1	25.4 months	4.7 months	<0.0001
		MS: RPA class 2	5.9 months	4.1 months	<0.04
		MS: RPA class 3	4.2 months	2.5 months	NS
Lee et al., 2008 (18)/ retrospective cohort	1–12	MS	29 months	6 months	0.0061
Wang et al., 2002 (43)/ retrospective cohort	1–6	MS	67 weeks	37 weeks	<0.00001†
		1-month LC rate	93.3%	88.3%	NR†
Li et al., 2000 (19)/ prospective cohort	1	MS	9.3 months	5.7 months	<0.0001‡
		Tumor response rate	87%	48%	0.004‡
		Local recurrence time	6.9 months	4 months	0.0000‡
		Distant recurrence time	6.7 months	4.1 months	0.0000‡
Datta et al., 2004 (6)/ retrospective cohort	BM	1-year survival rate	22.6%	26.3%	NS
		Mean survival	6.7 months	7.8 months	NS

BM, brain metastases; DC, distant control; IC, intracerebral control; LC, local control; MS, median survival; NR, not reported; NS, nonsignificant; OC, overall control; RPA, recursive partitioning analysis; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

*Data include surgery with WBRT and surgery plus WBRT plus SRS boost treatment arms.

†Data include surgery alone and SRS with WBRT treatment arms.

‡Data include SRS with WBRT treatment arm.

and 67 patients were treated with WBRT. The 1-year survival rate was 26.3% (mean of 7.8 months) for the WBRT group and 22.6% (mean of 6.7 months) for the GK group. Based on the given data, there was no statistical significance between the GK and WBRT groups in survival time. However, the authors concluded that 89% of patients treated with GK radiosurgery had lesions that were reduced, stabilized, or disappeared, but this high level of tumor control did not produce longer periods of survival.

Stereotactic Radiosurgery with or Without WBRT

An area of controversy in the treatment of patients with metastatic brain tumors is whether or not the addition of WBRT to SRS will provide patient groups with a better prognosis when compared with patient groups treated with SRS alone. We evaluated 2 randomized trials (2, 3), 1 prospective cohort study (19), and 10 retrospective cohort studies (4, 5, 8, 9, 13, 17, 29, 39, 41, 43) to investigate this question (**Table 5**). Studies by Li et al. (19) and Fokas et al. (8) are 3-arm studies, assessing patient groups treated with SRS alone, WBRT alone, and SRS with WBRT. The study by Wang et al. (43) was a 4-arm study that compared patients treated with SRS alone, WBRT alone, surgical resection alone, and SRS with WBRT. All 13 of these studies have been published since the year 2000.

The first randomized trial was published in 2006 by Aoyama et al. (2). A total of 132 patients with 1 to 4 brain metastases ≤30 mm in diameter who had a KPS ≥70 were eligible for the study. Precisely, 67 patients were randomized into the SRS-alone treatment arm and 65 patients were randomized into the SRS with WBRT treatment arm. The median time of survival for the SRS-alone group and SRS with WBRT group was 8 months and 7.5 months, respectively ($P = 0.42$). It was reported that the 12-month brain tumor recurrence rate ($P < 0.001$) and the frequency in which patients underwent salvage therapy ($P < 0.001$) statistically favored the SRS with WBRT treatment arm. The 2 groups did not differ in terms of death from neurological causes, toxicity, and functional preservation.

The most recent randomized trial, published in 2009 by Chang et al. (3), investigated whether the potential tumor control benefits of the addition of WBRT to SRS compensated for the potential toxicity associated with WBRT. The author's primary objective was to assess neurocognitive differences between the 2 treatment arms via the Hopkins Verbal Learning Test–Revised Scale at 4 months after treatment. There was a total of 58 patients with 1 to 3 brain

Table 5. SRS with or Without WBRT in the Treatment of Patients with Single or Multiple Brain Metastases

Author/Study Type	# BM	Study Endpoints	SRS	SRS/WBRT	*P* Value
Aoyama et al., 2006 (2)/ randomized	1–4	MS	8 months	7.5 months	NS
		1-year overall recurrence rate	46.8%	76.4%	<0.001
		Neurological death rate	19.3%	22.8%	NS
Chang et al., 2009 (3)/ randomized	1–3	1-year survival rate	63%	21%	0.003
		1-year LC rate	67%	100%	0.012
		1-year DC rate	45%	73%	0.02
		1-year CNS freedom recurrence rate	27%	73%	0.0003
Frazier et al., 2010 (9)/ retrospective cohort	BM	MS	8.3 months	8.5 months	NS
Li et al., 2000 (19)/ prospective cohort	1	MS	9.3 months	10.6 months	NS
		Tumor response rate	87%	89%	NS
		Median local recurrence time	6.9 months	8.6 months	NS
		Median distant recurrence time	6.7 months	8.6 months	0.0392
Sneed et al., 2002 (39)/ retrospective cohort	BM	MS	8.2 months	8.6 months	NS
Jawahar et al., 2002 (13)/ retrospective cohort	BM	MS	NR	NR	NS
		LC	NR	NR	NS
		Distant recurrence	NR	NR	NS
Varlotto et al., 2005 (41)/ retrospective cohort	BM	MS	NR	NR	NS
		1-year LC rate	84.1%	93.1%	
		3-year LC rate	68.6%	87.7%	0.0228*
		5-year LC rate	68.6%	65.7%	
		1-year DF rate	26%	20.7%	
		3-year DF rate	74.5%	49%	0.0657*
		5-year DF rate	74.5%	61.8%	
Fokas et al., 2010 (8)/ retrospective cohort	1–3	OS	12 months	16 months	NS
		RPA class 1 1-y IC rate	76%	100%	<0.001
		RPA class 2/3 1-y IC rate	39%	64%	0.039
Kong et al., 2010 (17)/ retrospective cohort	1–10	MS	272 days	351 days	NS
		MS: RPA class 1	426 days	854 days	0.042
		MS: RPA class 2	380 days	351 days	NS
		MS: RPA class 3	94 days	161 days	NS
		Median local recurrence time: RPA class 1	336 days	701 days	0.021
		Median local recurrence time: RPA class 2	325 days	295 days	NS
		Median local recurrence time: RPA class 3	NR	NR	NR
		Median distant recurrence time: RPA class 1	336 days	967 days	NS
		Median distant recurrence time: RPA class 2	292 days	311 days	NS
		Median distant recurrence time: RPA class 3	NR	NR	NR
Rades et al., 2008 (29)/ retrospective cohort	1–3	OS rate	53%	56%	NS
		IC control rate	51%	66%	0.015
		LC rate	66%	87%	0.003

Continues

Table 5. Continued

Author/Study Type	# BM	Study Endpoints	SRS	SRS/WBRT	*P* Value
Clarke et al., 2010 (5)/ retrospective cohort	1	OS	NR	NR	NS
		Local failure rate	22.7%	40%	NS
		Distant failure rate	68.2%	0%	NR
Wang et al., 2002 (43)/ retrospective cohort	1–6	MS	67 weeks	91 weeks	<0.001
		1-month LC rate	93%	96%	NR
Chidel et al., 2000 (4)/ retrospective cohort	BM	MS	10.5 months	6.4 months	NS
		Median local recurrence time	NR	NR	0.034
		Median distant recurrence time	NR	NR	NS
		Median overall recurrence time	9.2 months	35.1 months	0.027

BM, brain metastases; CNS, central nervous system; DC, distant control; DF, distant failure; IC, intracerebral control; LC, local control; MS, median survival; NR, not reported; NS, nonsignificant; OS, overall survival; RPA, recursive partitioning analysis; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
*Data collected on multivariate analysis.

metastases that were randomly assigned to an SRS-alone group (30 patients) and an SRS with WBRT group (28 patients) using a standard permutated algorithm. The study was stopped prematurely due to a very high probability (96%) that patients in the SRS with WBRT treatment arm would show worse neurocognitive deficits than the SRS-alone treatment arm at 4 months of follow-up (mean posterior decline probability of 52% vs. 24%). It was reported, however, that only 27% of patients in the SRS-alone group were free from central nervous system (CNS) tumor recurrence, whereas 73% of patients in the SRS with WBRT group were free from CNS tumor recurrence ($P = 0.0003$). Interestingly, patients in the SRS-alone treatment arm showed an increased period of survival, with a 1-year survival rate of 63% compared with 21% in the SRS with WBRT treatment arm ($P = 0.003$).

In the retrospective cohort study by Frazier et al. (9), the authors compared survival in 237 patients who were treated with either SRS alone or SRS with WBRT. It was reported that survival did not statistically differ between the 2 groups. However, patient groups that were <65 years of age ($P = 0.008$) with a KPS >70 ($P = 0.034$) were more inclined to survive a greater period of time than those who did not possess those characteristics. In the 3-arm prospective cohort study by Li et al. (19), 23 patients underwent SRS alone, whereas 18 patients were treated with SRS with WBRT. Similar to the prior study, the authors found that the 2 treatment arms did not show compelling statistical differences in terms of survival.

Of the 9 other retrospective cohort studies we reviewed, 6 found no statistically significant differences in survival between patient groups treated with SRS alone and those treated with SRS with WBRT (4, 5, 8, 13, 39, 41). Wang et al. (43) reported that the SRS with WBRT treatment arm had a survival advantage, living a median of 91 weeks, whereas patients treated with SRS alone survived a median of 67 weeks. In contrast, Chidel et al. (4) found a nonsignificant trend in survival ($P = 0.07$) that favored the SRS-alone treatment arm. Kong et al. (17) reported a statistically significant advantage in survival ($P = 0.042$) and local control ($P = 0.021$) in patients classified in RPA class 1 who were treated with SRS with WBRT, but this trend did not extend into patients classified in RPA class 2 or 3. Increased local control levels in the SRS with WBRT treatment groups were also reported in studies by Chidel et al. (4), Varlotto et al. (41), and Rades et al. (29). Improvements in distant brain control with the addition of WBRT were not as prevalent. Chidel et al. (4) ($P = 0.06$) and Varlotto et al. (41) ($P = 0.0657$) both witnessed nonsignificant trends in distant brain control favoring the SRS with WBRT treatment arm. Clarke et al. (5) reported that 55.6% of patients in their study showed distant brain failure. Two of the 9 studies (8, 29) found increased intracerebral control levels with the addition of WBRT to the SRS treatment regimen. These data permit the close monitoring of patients treated with either modality after treatment so that salvage therapy may proceed as soon as possible.

Stereotactic Radiosurgery Alone Compared with Surgery Plus WBRT

We reviewed 1 randomized trial and 1 retrospective cohort study comparing patient groups treated with neurosurgical resection with WBRT and patient groups treated with SRS alone. The randomized trial was conducted by Muacevic et al. (23) in 2008. A total of 64 patients with a single surgically accessible brain metastasis ≤30 mm in diameter, a KPS ≥70, and a stable primary cancer were randomly assigned to a surgery with WBRT group (33 patients) and an SRS-alone group (31 patients). Unfortunately, the study was stopped at the 25% accrual point. The authors did report, however, that the 2 treatment arms did not show statistically significant differences in survival, death due to neurological causes, or freedom of local tumor recurrence. The SRS treatment arm experienced a larger amount of distant tumor recurrences ($P = 0.04$), but this difference diminished after salvage therapy was conducted. It was also observed that patients encountered toxicities more frequently in the surgery with WBRT group ($P \leq 0.01$).

Rades et al. (28) analyzed 260 patients classified in RPA class 1 and 2 who possessed 1 to 2 metastatic brain tumors ≤40 mm in diameter. A total of 94 patients were treated with SRS alone, whereas 112 patients were treated with surgical resection followed by WBRT. The authors reported that the 2 treatment arms did not show statistically significant differences in terms of survival, overall brain control, or local tumor control. Data regarding death from neurological causes were not assessed.

STEREOTACTIC RADIOSURGERY TREATMENT PLANNING

Modes of Delivery

There are 3 devices currently used for SRS delivery: GK radiosurgery, linear accelerator (LINAC)-based treatment, and a cyclotron-based proton beam. The cyclotron-based proton beam is used by very few institutions because it is very expensive and requires a great deal of space and maintenance (12). The LINAC machine functions by accelerating an electron at a metal target, which produces an x-ray beam that is focused on a precise target by micromultileaf collimators (40). The GK device's main functional unit is cobalt-60, which is used to emit photon energy through 201 separate 4- to 18-mm collimator openings that ultimately converge on a focal point specified through computer planning (40). GK radiosurgery and LINAC-based treatment are known to produce equivalent patient outcomes. Published reports by Andrews et al. (1) and Sneed et al. (39) both concluded that mode of SRS delivery did not influence patient prognosis.

Dosing

In 2000, the RTOG published a study investigating the maximum tolerated dose of single-fraction radiosurgery that was led by Shaw et al. (38). A total of 156 patients with recurrent brain metastases (64%) and primary brain tumors (36%) were assessed. The authors concluded that the maximum tolerated doses for tumors ≤20 mm was 24 Gy, 18 Gy for tumors 21 to 30 mm in diameter, and 15 Gy for tumors 31 to 40 mm in diameter, respectively. Patients with tumors >20 mm in diameter were 7.3 to 16 times more likely to encounter grade 3 to 5 toxicities when compared with patients who possess tumors ≤20 mm in maximum diameter. At the Gamma Knife of Spokane, we follow the guidelines diagrammed by the RTOG and prescribe a maximum dose of 20 to 24 Gy for metastatic tumors ≤20 mm in diameter, based on previous radiation therapy the patient has undergone and the proximity of critical structures. For tumors 21 to 30 mm in diameter and 31 to 40 mm in diameter, maximum doses of 18 Gy and 15 Gy are prescribed. These doses may be altered; thus, each specific patient's treatment is unique.

Table 6. RPA Categorization (10)

RPA Class 1	
	KPS ≥70
	Controlled first-degree cancer
	<65 years of age
	Extracranial disease is not present
RPA Class 2	
	KPS ≥70
	Uncontrolled first-degree cancer *and/or*
	≥65 years of age *and/or*
	Extracranial disease is present
RPA Class 3	
	KPS <70

KPS, Karnofsky Performance Score; RPA, recursive partitioning analysis.

Variables Influencing Patient Advantage

The most common method of categorizing patients who suffer from metastatic brain tumors is the RTOG RPA prognostic system (10) (**Table 6**). The patient's age, KPS, control of primary cancer, and presence of extracranial metastases are all taken into account to assign the patient into 1 of 3 RPA classes, with a higher class statistically indicating a worse prognosis for the patient in question. Patient outcomes after SRS are influenced by the 4 criteria diagrammed by the RTOG, as well as 3 other factors: the number, location, and size of the patient's metastases. With the numerous combinations of treatment modalities that exist today for patients with brain metastases, these 7 variables must be assessed together to prescribe the optimal course of treatment in desired patients.

Toxicity

The most common acute side effects occurring after SRS are caused not by the radiation, but by the stereotactic head-frame that is attached to the patient's skull. These include headaches after the stereotactic head-frame is removed and screw-site soreness at the areas where the head-frame was attached to the patient's skull (40). Acute toxicities (**Table 7**) that result from the radiation are seizures and the worsening of neurological symptoms for a relatively short period of time (37). Studies by Aoyama et al. (2) and Lutterbach et al. (21) both concluded that long-term side effects occurring after SRS are less common in treated patients than acute toxicities. However, a small fraction of patients will experience long-term side effects that range from radiation necrosis, edema, the development of new neurological deficits, and the exacerbation of neurological deficits the patient has previously suffered from (40). Caution must be taken with the use of steroids because they are also known to come with a variety of side effects.

Table 7. Toxicities Associated with SRS

Acute Side Effects	
	Headaches
	Screw-site soreness
	Seizures
	Infection at screw site
	Worsening of neurological symptoms
Long-Term Side Effects	
	Radiation necrosis
	Edema
	New neurological deficits
	Worsening of existing neurological deficits

CONCLUSIONS

After assessing patient age, KPS, control of primary cancer, presence of extracranial metastases, number of brain metastases, location of brain metastases, and size of brain metastases, SRS offers suitable patients a viable, less invasive treatment option. In patients with 1 to 4 brain metastases who have a KPS ≥70, the addition of SRS to WBRT produces increased levels of survival and local tumor control when compared with patients treated with WBRT alone. The available evidence suggests that patients treated with SRS alone show superior levels of survival and tumor control with fewer cognitive side effects when compared with patients treated with WBRT alone. Evidence in the form of a phase III randomized trial is needed to confirm this published evidence. Many unanswered questions remain regarding survival and tumor control in patient groups treated with SRS with or without WBRT. Recently published randomized evidence reported a survival advantage in patients treated with SRS alone. These data differ from previously published randomized evidence, as well as several prospective and retrospective studies that reported nonsignificant survival differences. Contrasting evidence also exists pertaining to local and distant tumor control that warrants further investigation into this controversial matter.

The available evidence suggests that in patients with 1 to 2 brain metastases, both SRS alone and SRS with WBRT offer equivalent levels of survival when compared with patients treated with surgery with WBRT. Research has been conducted that reports a survival advantage in specific patient subsets with 1 to 3 brain metastases that were treated with SRS with WBRT. Inconsistent results have been reported for these groups regarding local and distant tumor control levels. Further analysis and research must be conducted for this patient group and for patients with ≥3 brain metastases.

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