

RADIOSURGERY IN METASTATIC BRAIN CANCER

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RADIOSURGERY OFFERS PATIENTS with brain metastases an effective and minimally invasive treatment modality. Radiosurgery provides local tumor control and prolongs survival in select patients with brain metastases. This review will discuss numerous aspects of radiosurgery, including the various delivery techniques and radiobiology. Treatment recommendations will be outlined in view of the available clinical data. Although surgery or radiosurgery with whole-brain radiotherapy remains an important option for patients with a solitary brain metastasis, radiosurgery with or without whole-brain radiotherapy should be considered in patients with a limited number of small tumors and a good prognosis.

KEY WORDS: Brain metastases, Fractionated stereotactic radiotherapy, Gamma Knife, Linear accelerator, Particle beam, Radiobiology, Radiosurgery

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Focal treatment of brain metastases with surgical resection has been shown to improve local tumor control and to prolong survival, particularly when combined with whole-brain radiotherapy (WBRT) (see Chapter 4 for more information). Surgery with or without WBRT remains an important option for select patients with a solitary brain metastasis (46, 47). However, surgical resection may be contraindicated for many patients because of comorbid conditions or unresectable locations.

For more than 30 years, radiosurgery (RS) has provided patients who have brain tumors an alternative focal treatment to surgery. Initially, only benign tumors, such as meningiomas and acoustic neuromas, were selected for treatment with RS. However, in the last 15 years, RS as a therapeutic option was also considered for patients with brain metastases who had controlled systemic disease and/or a good prognosis because of systemic therapies that are more effective.

RS combines the principles of stereotaxy with focal radiation delivery techniques using photons or charged particles. Computed tomography (CT) and magnetic resonance imaging (MRI) are used to precisely localize tumors in three dimensions. In a single session, multiple beams of radiation from a high-energy source are used to produce a conformal treatment plan that allows delivery of high radiation doses to the target while limiting exposure to normal brain tissue. Studies

have shown that RS is effective at controlling brain metastases and prolonging survival (20, 24, 36, 40, 50). Moreover, RS is minimally invasive and can be performed on an outpatient basis, which has implications for quality of life issues and health care economics, compared with surgery. However, to our knowledge, RS has never been compared with surgery for patients with brain metastases in a prospective clinical trial. A number of studies have retrospectively compared RS and surgery with conflicting results (see Chapter 7 for more information) (6, 9, 39, 52).

As our understanding of prognostic factors for patients with brain metastases has improved and treatment has become individualized, RS has become a common form of therapy in selected patients. However, many treatment issues remain unresolved, such as the use of RS with or without WBRT and its value compared with other treatment modalities. This review will discuss the role of RS in the management of brain metastases. The various delivery techniques and radiobiology will be discussed, as well as treatment guidelines in view of Class I, Class II, and Class III data.

DELIVERY TECHNIQUES

The most commonly used RS systems are the Gamma Knife (Leksell Gamma Knife®, Elekta Instrument AB, Inc., Stockholm, Sweden) and the linear accelerator (LINAC). The Gamma

Knife is designed to treat intracranial targets only. The head is immobilized with a stereotactic frame and imaging with a fiducial localizing box is performed using thin CT or MRI slices with contrast. After the treatment planning is completed, delivery is conducted by placing the patient in a secondary head collimator unit with circular apertures of 4, 8, 14, and 18 mm. When aligned with the primary source unit, converging radiation beams from 201 cobalt-60 sources can be centered at the desired target for each planned isocenter. Multiple isocenters are used to cover the target volume and develop a conformal treatment plan. Different sized collimators, beam blocking, and multiple isocenters modify the isodose distribution, and delivery is accomplished using automated and/or manual patient positioning.

The LINAC system uses x-ray beams and uses a stereotactic frame, with or without pin fixation. The radiation beam can be shaped to the target by manipulating arc angles, using multiple isocenters, differentially weighting the isocenters, and using blocks, collimators, and multileaf collimators. In multileaf collimator units, the beam aperture can also be modified dynamically during rotation of the gantry around an isocenter. Robotically controlled accelerators, with static collimators, can direct beams from a large number of non-coplanar directions and can vary the dwell time for each beam, effectively modulating the dose across the target volume. In addition, the LINAC system can be used to treat other body sites and for fractionated stereotactic radiotherapy (FSR). Whereas a high dose of radiation is delivered in a single session with RS, patients are treated with moderate dose fractions during multiple sessions with FSR. FSR may be preferred for patients who cannot tolerate high doses of radiation or for patients with metastases too large for RS (27, 34, 55, 63).

Although there are advantages and disadvantages for the LINAC and Gamma Knife systems, they do not seem to be clinically relevant (4, 7, 51). A Radiation Therapy Oncology Group (RTOG) study (RTOG 9005) reported better local brain tumor control for the Gamma Knife over the LINAC (53). However, this study was not randomized, and the study population included patients with recurrent primary or metastatic brain tumors, therefore, these results are difficult to interpret. A more recent randomized trial by the RTOG (RTOG 9508) found no survival difference between the two systems when used as a boost to WBRT (4).

Particle beam systems use charged-particle beams produced by a cyclotron or synchrotron (23, 35, 49). The dose distribution with charged particles can theoretically be superior to that derived using photon delivery systems, especially for large targets or those close to critical structures. Photons derived from any source lack charge and mass compared with particles, and cannot be made to stop at a defined position, therefore, the build-up of a target dose relies primarily on the accurate intersection of beams at the target. The number of beams used, the size and shape of beams, and the prescribed dose also determine how much energy is deposited in tissues before or beyond the desired target. Charged particles, such as protons, have a much greater mass compared with photons, and can be energized to specific velocities. This determines how deeply the particles penetrate the body and where the

maximum energy (i.e., the Bragg peak) is deposited. Because of this terminal interaction of the incident particle with the target tissue, there is minimum deposition of dose beyond the target. Magnets, alternating beam energy, occluding rings, and collimators are used to target and conform the dose. Published data in brain metastases are limited for particle beam systems. Despite the apparent advantages of the charged-particle systems, few centers currently have these systems, because of their expense. Few are available for clinical use compared with LINAC and Gamma Knife units.

In the past, radiation beam shape was a rectangular or circular field, which made it difficult to conform the radiation dose to irregularly shaped tumors. Such tumors often required multiple isocenters, which increased the dose heterogeneity and the likelihood of side effects and morbidity (43). Recent advances in RS have focused on improving conformity between the dose and the target volumes (44). Advances in imaging and treatment-planning software have improved tumor localization, targeting, and the accuracy of dose calculations. Mechanical advances also have occurred. One commercially available LINAC-based system (CyberKnife; Accuray, Sunnyvale, CA) uses a robotic arm in conjunction with an image-guided localization system that tracks patient position to aim the radiation beams from various angles so that a stereotactic frame is unnecessary. The development of multileaf collimators for use with the LINAC system has greatly improved the conformity of dose and target volumes compared with conventional static spherical collimators, reduced the need for multiple isocenters, and decreased the radiation to normal brain tissue (56).

An emerging system that uses multileaf collimators is intensity-modulated radiation therapy. In static intensity-modulated radiation therapy, beams of radiation are shaped and modulated by rapidly opening and closing collimator leaves, which creates a heterogeneous radiation field from a single angle. Multiple beams from various angles converge, so that the prescribed dose more tightly conforms to the target volume. This minimizes the dose to normal tissue while delivering higher radiation doses to the target. Although limited data are available for the use of intensity-modulated radiation therapy in brain tumors (65), its principles are now being applied to intensity-modulated RS, with promising results from treatment-planning studies (41).

RADIOBIOLOGY

Part of the rationale for using RS rather than WBRT is that a high local dose of radiation in a single fraction will produce better tumor control, which will translate into longer survival. In fact, studies have shown that metastases resistant to WBRT (i.e., sarcoma, melanoma, and renal cell carcinoma) can be successfully treated with RS (1, 11). The object of RS in treating brain metastases is to deliver a high dose of radiation to a target volume, destroying all cells within the target boundaries. Typical doses to the margins of the tumor range from 15 to 20 Gy, with higher doses at the target center. Dose depends, in part, on tumor size, location, and previous radiation treat-

ments. Tumor control may be achieved by direct early effects (apoptosis or mitotic death), by late vascular changes, and/or by the stimulation of the immune response (30, 59).

Brain metastases are well suited for RS. They are often small, radiographically well-circumscribed, pseudospherical tumors that are noninvasive, and they are often located at the gray-white junction, where toxicity to critical structures is low (25). Because of this, brain metastases are treated as distinct targets without intermingling of normal tissue. The high RS dose is delivered to a discrete target volume with a sharp fall off at the target boundaries, so that adjacent normal tissue receives a clinically insignificant dose of radiation. This substantially improves the therapeutic ratio (probability of tumor control to probability of complications) of RS.

There are important caveats. Tight conformation of the prescribed dose to a tumor volume increases the risk of dose heterogeneity, particularly when multiple isocenters are used for large and/or irregularly shaped tumors (44, 66). It is not known whether dose homogeneity within the target volume of a metastasis (which is solid tumor tissue without infiltrated normal tissue) is clinically important. Underdosage (cold spots), particularly at the tumor margins, may result in incomplete ablation of tumor cells, thus, increasing the risk for tumor recurrence; and overdosage (hot spots) may expose brain tissue to excessive radiation, increasing the risk of sequelae. This is particularly relevant for tumors located near critical structures, such as the optic chiasm, which has a tolerance dose of 8 Gy for a single irradiation (62). Furthermore, as the number of targets increase, so does the irradiated volume and dose to normal brain tissue (60).

Tumor size also affects the therapeutic ratio. A dose escalation study by the RTOG demonstrated that the maximum tolerated RS dose for brain tumors was directly related to the tumor size (53). As shown in *Figure 5.1A*, an RS dose of 18 Gy resulted in neurotoxicity rates of 8, 20, and 50% in patients with tumor sizes of 20 mm or less, 21 to 30 mm, and 31 to 40 mm, respectively. Using a cut-off toxicity rate of 20%, the RTOG investigators determined that the respective maximum tolerable doses were 24 Gy (cut-off was not reached), 18 Gy, and 15 Gy for tumors of less than 20 mm, 21 to 30 mm, and 31 to 40 mm. In addition, a study by Mehta et al. in patients with metastatic brain tumors showed that, as tumor size increased, control decreased (*Fig. 5.1B*) (38). Patients with treated tumors of less than 2 cm³ had complete and partial response rates of 61% and 17%, respectively; whereas patients with tumors of greater than 10 cm³ had rates of 10% and 40%, respectively. For success in treating brain metastases with RS, it is essential that: 1) tumors are precisely localized; 2) the dose distribution is conformal; and 3) the maximum tolerated dose based on tumor size and position is administered for the greatest antitumor effect.

CLINICAL EVIDENCE

Nonrandomized Prospective and Retrospective Studies (Class II and III Data)

The majority of evidence supporting the use of RS in brain metastases comes from nonrandomized trials (Class II data)

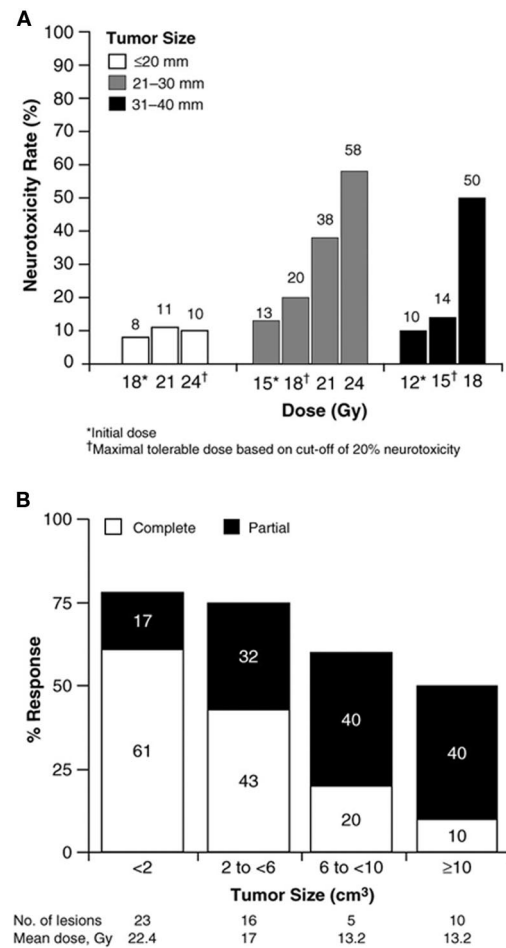


FIGURE 5.1. A, effect of brain tumor size on complications in patients treated with RS (from, Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, Farnan N: Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys* 47:291-298, 2000 [53]). B, effect of brain tumor size on local control in patients treated with RS (from, Mehta MP, Rozental JM, Levin AB, Mackie TR, Kubsad SS, Gehring MA, Kinsella TJ: Defining the role of radiosurgery in the management of brain metastases. *Int J Radiat Oncol Biol Phys* 24:619-625, 1992 [38]).

and retrospective studies (Class III data). *Table 5.1* summarizes data from nonrandomized trials and retrospective studies that included more than 100 patients (1, 12, 17, 19, 20, 24, 26, 28, 36, 40, 48, 50). These data suggest that RS is more effective than WBRT and comparable to surgery (39, 46, 47). Median survival was greater than 6 months in all but one study (50), ranging from 5.5 to 13.5 months. Local tumor control with RS was consistently greater than 80%; however, this did not translate into improved survival, because corresponding survival rates were notably lower (12, 19, 24, 26, 36, 48, 50). In fact, the majority of patients in these studies died of systemic-disease progression (20, 36, 40, 50).

TABLE 5.1. Nonrandomized and retrospective studies in patients with brain metastases treated with radiosurgery^a

Series (ref. no.)	Type of RS	No. of patients/lesions	Primary tumor type	Tumor diameter (cm)	KPS score	Dose (Gy) ^b	Local control (%) ^c	Survival at 1 yr (%)	Median survival (mo)	CNS death (%)
Nonrandomized, prospective studies										
<i>Gerosa et al., 1996 (20)</i>	Gamma knife	152/236	Various			21.2	88		9.3	30
<i>Pirzkall et al., 1998 (50)</i>	LINAC	236/311	Various	≤3.8	≥50	15–20	92		5.5	
<i>Lutterbach et al., 2003 (36)</i>	LINAC	101/155	Various	≤3.0	≥50	18	91	27	7.6	
<i>Hasegawa et al., 2003 (24)</i>	LINAC	172/218	Various	≤3.5	≥50	20	87	36	8	11
<i>Muacevic et al., 2004 (40)</i>	Gamma knife	151/620	Breast cancer	≤3.0	≥40	19	94		10	27
Retrospective studies										
<i>Flickinger et al., 1994 (17)</i>	Gamma knife	116/116	Various	≤3.6		17.5	85		11	
<i>Alexander et al., 1995 (1)</i>	LINAC	248/421	Various	≤4.0	≥70	15	85		9.4	31
<i>Joseph et al., 1996 (28)</i>	LINAC	120/189	Various		≥50	26.6	96		8	19
<i>Chen et al., 2000 (12)</i>	Gamma knife	190/431	Various	≤3.0	≥70	20	89	32	8.5	38
<i>Hoffman et al., 2001 (26)</i>	Gamma knife	113/301	Lung carcinoma	≤3.0	≥50	18	81	48	12	23
<i>Gerosa et al., 2002 (19)</i>	Gamma knife	804/1307	Various		≥60	20.6	93	62	13.5	16
<i>Petrovich et al., 2002 (48)</i>	Gamma knife	458/1305	Various	≤3.5	≥70	18	87	33	9	

^a RS, radiosurgery; KPS, Karnofsky performance status; CNS, central nervous system; LINAC, linear accelerator.

^b Median, mean prescription, or median peripheral dose.

^c Reported as crude local control, actuarial local control, or freedom from progression.

In addition to systemic-disease status, other factors may contribute to the discrepancy between the high rate of local tumor control and the corresponding survival. Table 5.2 summarizes prognostic factors for survival and local tumor control. Absence of extracranial disease, higher Karnofsky Performance Status (KPS) score, and younger age were associated with prolonged survival in several studies (24, 36, 40, 50). Not surprisingly, RTOG recursive partitioning analysis (RPA) Class 1 patients (patients with a KPS score ≥70, age ≤65 yr, no extracranial metastases, and controlled systemic disease) was associated with longer survival (24, 36, 40).

Although some of these prognostic data will require confirmation, they should be noted, particularly regarding primary tumor type. Lutterbach et al. (36) reported that renal cancer was associated with a reduced risk of death compared with other primary tumor types (relative risk, 0.59; 95% confidence interval, 0.39–0.84; *P* = 0.002); whereas retrospective studies by Flickinger et al. (17) and Petrovich et al. (48) reported better survival for patients with metastatic breast cancer. Hasegawa et al. (24) found that metastatic melanoma was associated with poorer survival (*P* = 0.0046) than other metastatic tumor types. Because of the high rate of systemic-disease death, it is difficult to interpret these results.

Chen et al. (12) and Petrovich et al. (48) estimated a wide range for median survival by primary cancer type, whereas Sneed et al. (57) showed more uniform survival times (Table 5.3). Interestingly, Petrovich et al. (48) showed a higher CNS-disease death rate in metastatic melanoma than in other primary tumor types (42% versus 23%). Chen et al. (12) also reported a high CNS-disease death rate in metastatic melanoma (44%), whereas death from CNS disease-related causes

was uncommon for renal or colon cancer. Further analyses of CNS-disease death rates and tumor control by primary cancer type may better clarify the benefit of RS for certain brain metastases.

Studies have also identified factors associated with tumor control. Flickinger et al. (17) reported that metastatic melanoma and renal cancer were associated with better tumor control than other primary cancer types. Other factors that may influence tumor control include tumor volume (12, 24, 48), location (infratentorial versus supratentorial) and presentation (new versus recurrent) (1), and pattern of enhancement on MRI (homogeneous versus heterogeneous versus ring pattern) (22, 26, 54).

In addition, Chen et al. (12) and Flickinger et al. (17) found that adjunct WBRT improved local control, but this did not seem to translate into improved survival. The use of adjunct WBRT with RS has been somewhat controversial because the benefit seems to be limited to improved tumor control, whereas its use is associated with serious late-term complications, such as dementia (14). Although randomized surgical studies have demonstrated a clear survival benefit with adjunct WBRT (46), retrospective studies indicate that the addition of WBRT to RS does not significantly improve survival (57, 58). In view of the serious long-term side effects associated with WBRT plus RS (28), some investigators have suggested that WBRT should be omitted in patients undergoing RS. Conversely, others have argued that the addition of WBRT improves control of cerebral metastases, which, in turn, may preserve or improve neurological function (45). Furthermore, the long-term toxicity of WBRT may not be as common as once thought, and late-term complications may not be as relevant to brain metastases because of the limited survival time (45).

TABLE 5.2. Prognostic factors for survival and tumor control^a

Factor	Class II	Class III
Survival		
<i>RPA Class 1</i>	(24, 36, 40)	(58)
<i>Higher KPS score</i>	(24, 36, 50)	(12, 26, 28, 48, 57)
<i>Controlled systemic disease</i>	(24, 36, 50)	(1, 12, 26, 48)
<i>Younger age</i>	(24, 50)	(1)
<i>Lower tumor number</i>		(26, 28)
<i>Primary tumor type</i>		
<i>Breast (versus others)</i>		(17, 48)
<i>Melanoma (versus others)^b</i>	(24)	
<i>Renal (versus others)</i>	(36)	
Tumor control		
<i>Smaller tumor size</i>	(24)	(12, 48)
<i>Lower tumor number</i>	(36)	
<i>Longer time to brain metastases</i>	(36)	
<i>Adjunct WBRT</i>		(12, 17)
<i>Supratentorial location (versus infratentorial)</i>		(1)
<i>New lesion (versus recurrent)</i>		(1)
<i>Type of primary tumor</i>		
<i>Breast</i>		(22)
<i>Melanoma (versus others)</i>		(17)
<i>Renal cell (versus others)</i>		(17, 22)
<i>Homogeneous pattern of enhancement</i>		(22)
<i>Higher radiosurgical dose</i>		(22, 26, 54)

^a Factors associated with prolonged survival and tumor control, unless otherwise noted. RPA, reverse partitioning analysis; KPS, Karnofsky Performance Status; WBRT, whole-brain radiotherapy.

^b Associated with shorter survival time.

Pirzkall et al. (50) compared the use of RS alone with RS plus WBRT in a series of 236 patients with brain metastases (n = 158 for RS alone, n = 78 for RS plus WBRT). The use of RS plus WBRT showed a trend for improved local control with 1-year and 2-years actuarial control rates of 92% and 86%, respectively, compared with 89% and 72% for RS alone (P = 0.13). Median survival for the entire study population was 5.5 months, and 1-year and 2-years survival rates did not significantly differ between the treatment groups. However, survival was significantly longer in patients without extracranial disease versus those with extracranial disease (12.5 mo versus 4.4 mo; P < 0.001), and further analysis of the subgroup without extracranial disease demonstrated a survival advantage for RS plus WBRT versus RS alone (15.4 mo versus 8.3 mo; P = 0.08).

Retrospective studies by Sneed et al. (57) found that the omission of adjunct WBRT at the time of RS treatment did not compromise survival for patients with brain metastases. The first study reviewed data from 62 patients treated with RS alone and 43 patients treated with RS plus WBRT. Median survival was similar between RS alone and RS plus WBRT (11.3 mo for RS alone versus 11.1 mo for RS plus WBRT; P = 0.8). Local tumor control at 1 year did not significantly differ

between treatment groups (71% versus 79%, respectively; P = 0.3), whereas distant tumor control favored the RS plus WBRT group (37% versus 80%, respectively; P = 0.03), as did intracranial (local and distant) tumor control (28% versus 69%, respectively; P = 0.03). However, in a subgroup of patients who received salvage therapy, intracranial tumor control at 1 year did not differ between the RS-alone group versus the RS-plus-WBRT group (62% versus 73%; P = 0.56). A second study, also retrospective, compared 268 patients treated with RS alone with 301 patients treated with RS plus WBRT. There was no survival difference between the treatment groups for the overall population or by RPA class (58).

The studies by Petrovich et al. (48) and Sneed et al. (57) suggest 1) that the use of RS plus WBRT may prolong survival, provided that systemic disease is controlled, and 2) that delaying WBRT does not

seem to compromise survival, and that some form of salvage treatment can provide effective tumor control if recurrence after RS does occur. Clearly, randomized trials are needed to better understand the use of adjunct WBRT with RT. Interim results from a randomized control trial (n = 61) comparing RS alone versus RS plus WBRT did not confirm a survival benefit with the addition of WBRT (1-yr actuarial survival rate, 26% versus 39%; P = 0.58); and freedom from new brain metastases at 6 months was significantly greater with combination therapy (49% versus 82%; P = 0.003), as was 1-year local tumor control (70% versus 88%; P = 0.019) (5). An ongoing Phase III randomized trial by the European Organisation for Research and Treatment of Cancer (EORTC 22952), will compare the use of adjunct WBRT versus no adjunct therapy after surgical resection or RS (15). Unfortunately, the American College of Surgeons Oncology Group (ACOSOG-Z0300), a Phase III randomized trial comparing RS with or without WBRT, was closed because of lack of accrual of patients (3).

Randomized Trials (Class I Data)

Two randomized trials have assessed the use of RS as a boost to WBRT. A study at the University of Pittsburgh by

TABLE 5.3. Median survival by primary tumor type^a

Primary tumor type	Chen et al., 2000 (12)		Sneed et al., 2002 (58)		Petrovich et al., 2002 (48)	
	No. of patients	Median survival (mo)	No. of patients	Median survival (mo)	No. of patients	Median survival (mo)
Melanoma	88	6.9	93	7.1	231	8
Breast	12	16.6	50	8.6	38	17
Colon	9	5.3			13	6
Lung			282	8.7	94	9
NSCLC	40	9.7				
SCLC	5	2.8				
Renal	49	12.3	62	9.6	29	12
Other	24	5.4	82	8.4	39	6

^a NSCLC, non small cell lung cancer; SCLC, small cell lung cancer.

Kondziolka et al. (32) compared WBRT alone (30 Gy/12 fractions) with WBRT plus RS (tumor margin dose of 16 Gy). The trial was stopped at the interim analysis with 60% accrual; 27 patients with two to four brain metastases were randomized (14 patients to WBRT and 13 to WBRT plus RS). The use of RS significantly improved brain tumor control. Local failure at 1 year was 8% for WBRT plus RS, versus 100% for WBRT alone, with a median time to local failure of 36 months versus 6 months ($P = 0.0005$). Median time to any brain failure (local or newly distant tumors) was also significantly longer for WBRT plus RS versus WBRT alone (34 mo versus 5 mo; $P = 0.002$). Despite this improved control, median survival did not differ by treatment (11 mo versus 7.5 mo, respectively; $P = 0.22$). The majority of patients died from progression of extracranial disease. Some patients in the WBRT-alone group eventually received salvage RS. If these patients were removed from analyses, a significant survival improvement was shown for the WBRT-plus-RS group compared with the WBRT-alone group ($P = 0.028$). Treatment complications included mild scalp erythema and hair loss for patients receiving WBRT.

A similar study, RTOG 9508, randomized 333 patients with one to three brain metastases to WBRT (37.5 Gy/15 fractions) or WBRT plus a RS boost (1). The RS dose depended on tumor size and ranged from 15 to 24 Gy. Treatment-related complications were infrequent (1% for WBRT plus RS versus 0% for WBRT alone). Mean survival was similar between the groups (6.5 mo for WBRT plus RS versus 5.7 mo for WBRT alone; $P = 0.1356$), as was the rate of neurological death (28% versus 31%, respectively). Systemic disease was the cause of death in more than half of the patients. Local control at 1 year was significantly better for WBRT plus RS versus WBRT alone (82% versus 71%; $P = 0.01$), and time to local progression was significantly shorter ($P = 0.0132$) for the WBRT-alone group. Time to intracranial progression (local and distant) did not differ between the treatment groups ($P = 0.1278$). An analysis of performance showed that

mental status was similar between the treatment groups at 6 months. However, a greater number of patients had an improved KPS score after WBRT plus RS versus WBRT alone (10 patients versus 3 patients; $P = 0.0331$), and corticosteroid usage decreased in significantly more patients (41 patients versus 25 patients; $P = 0.0158$).

Subgroup analyses provided several interesting results (1). Mean survival was significantly longer for WBRT plus RS versus WBRT alone for patients with single metastases (6.5 mo versus 4.9 mo; $P = 0.0390$), but did not differ for patients with multiple metastases (5.8 mo versus 6.7 mo; $P = 0.9776$). RS boost also improved survival versus WBRT alone in other subgroups, including RPA Class 1 patients (11.6 mo versus 9.6 mo; $P = 0.0453$), and patients with tumors 2 cm or greater in diameter ($P = 0.0449$), and significance was nearly achieved in patients with squamous cell or nonsmall cell lung cancer ($P = 0.0508$). There was no difference in survival for the overall population when stratified by RS system (LINAC versus Gamma Knife), and RS dose did not affect survival. Multivariate analysis showed that RPA Class 1 and metastatic lung cancer were significant predictors of prolonged survival.

Results from the Pittsburgh and RTOG studies demonstrated that the combination of RS and WBRT is more effective than WBRT alone. The RTOG concluded that WBRT plus RS should be standard treatment for patients with a single unresectable metastasis. For patients with two to three metastases, these results also suggest that use of combination therapy be considered. The addition of RS to WBRT improved performance for all patients, and local control and was not associated with increased risk for complications. Despite these benefits, survival remained limited because of systemic-disease progression.

COMPLICATIONS

RS is well tolerated and usually can be performed on an outpatient basis. Treatment-related complications are relatively infrequent and generally moderate in severity. Nausea, vomiting, alopecia, and headaches are the most common mild-to-moderate side effects (1, 10, 28). Complications that are more serious can be stratified by time of presentation. Acute side effects (those occurring hours to days after treatment) include headaches, nausea, vomiting, and seizures. Subacute side effects (occurring within the first 6 mo) include edema, deterioration of preexisting neurological deficits, and seizures (1, 17, 48, 54, 57). Radiation necrosis may occur subacutely but is usually a late complication (1, 10, 17, 28, 40, 50, 57). Larger tumors

and adjunct WBRT are associated with increased risk for complications (28, 37).

Varlotta et al. (64) analyzed tumor control and toxicity in patients who had survived for at least 1 year after RS. They found that post-RS sequelae developed in 2.8% and 11.4% of patients at 1 and 5 years after RS, respectively, and that the only factor significantly associated with late risks of complications was treatment volume. For tumors of 2 cm³ or less, the 1-year and 5-years incidence of complications was 2.3% and 3.7%, respectively. For tumors of 2 cm³ or greater, the incidences were 3.4% and 16%, respectively. In another study of patients treated with RS with or without WBRT, 200 consecutive patients were surveyed to assess the patients' perspective regarding complications (31). One hundred four (52%) of the 200 patients responded. Sixty-three percent of the patients who had WBRT and 36% of the patients who had RS reported side effects of treatment ($P < 0.001$). Hair loss, short-term memory problems, fatigue, long-term memory problems, concentration problems, and disorders of mood were much less common in the RS-only group.

Many of these complications can be effectively resolved. Edema can be treated with corticosteroids or, in more severe cases, with surgery. Corticosteroids are usually tapered and discontinued after edema is resolved, but some patients may require long-term treatment to control persistent edema (38). Radiation necrosis also can be treated with corticosteroids or surgery, and there is some anecdotal evidence that hyperbaric oxygen treatment is effective (13, 16, 29, 33). It is important to differentiate necrosis from tumor recurrence, which can be difficult with conventional CT or MRI. Positron emission tomography, magnetic resonance spectroscopy, and magnetic resonance blood volume mapping have been used to help make this distinction and guide clinical decisions. However, whether it is recurrent tumor or radiation necrosis, any patient with a symptomatic lesion that has failed corticosteroid treatment may require surgical resection. Historically, although anticonvulsants have been used prophylactically for patients with brain metastases (48), the American Association of Neurologists recommends that anticonvulsants should not be used routinely in patients with brain tumors because of the limited benefit versus potential side effects (21).

TREATMENT GUIDELINES

Currently, the National Comprehensive Cancer Network recommends RS plus WBRT as a treatment option for patients with brain metastases depending on the metastases locations, the systemic-disease status, the tumor and radiation history, and the number of metastases (42). For patients with a resectable new solitary metastasis or a symptomatic metastasis with mass effect, surgery followed by WBRT is recommended, whereas WBRT alone is the standard treatment for patients with active systemic disease and poor prognosis.

There are additional considerations for treating patients with RS. Generally, patients in RPA Class 1 have a favorable prognosis and should be treated aggressively, whereas patients in RPA Class 3 (KPS score <70) have a less favorable prognosis and palliative care may be more appropriate (18).

Because it is minimally invasive and can be performed on an outpatient basis, studies suggest that RS can be used for palliative care by targeting tumors associated with symptoms and affecting quality of life (2). For patients with a good KPS score and a limited number of metastases, RS should be considered when surgery is contraindicated. As discussed, it is important to take into account tumor size and number (38, 53). Generally, metastases 3 cm or less in diameter, without abundant surrounding edema can be treated with RS. For tumors less than 3 cm in diameter, surgical resection and WBRT should be considered. Focal external radiation is an option but may limit the ability to administer WBRT for salvage in the future because of overlapping fields and resulting excessive dose in normal tissues. Studies have demonstrated the effectiveness of RS in patients with multiple metastases (25, 32, 40, 68), but precautionary steps should be taken to optimize dose homogeneity and to limit exposure to normal tissue (60, 61, 67). Tumors that have been historically "radioresistant" to WBRT, such as metastatic melanoma and renal cell carcinoma, also should be considered for RS (1, 11). Before treating recurrent metastases with RS, diagnostic steps should be taken to differentiate recurrence from necrosis (8), and the irradiation history of the patient should be carefully reviewed. Studies have demonstrated that reirradiation with RS is safe and effective in selected patients (25, 53).

CONCLUSIONS

RS is a safe and effective therapy for patients with brain metastases. Although Class I data are limited, recent randomized trials provide evidence that the addition of RS to WBRT improves survival in patients with solitary metastases, improves local control in patients with two to four metastases and improves functional autonomy in all patients. A body of Class II and III data further supports the use of RS with WBRT or as a monotherapy, and suggests that efficacy is comparable to that of surgery. Surgery with WBRT should remain an important treatment option for most patients with a solitary, symptomatic, brain metastasis, until proven otherwise. An ongoing randomized trial will address the comparative efficacy of RS versus surgery, as well as the issue of adjunct WBRT use with RS. It is unclear whether the benefit-to-risk ratio of up-front WBRT with RS is more favorable than delayed WBRT. It is important to recognize that with current treatment modalities, survival will remain limited because of systemic disease progression.

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