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Stereotactic Radiosurgery: Indications and Outcomes in Central Nervous System and Skull Base Metastases

Henry Jeison Ruiz-Garcia, Daniel M. Trifiletti, and Jason P. Sheehan

Abbreviations

ASTRO	American Society for Radiation Oncology
CDFS	Cognitive Deterioration Free Survival
CP	Cognitive preservation
CSF	Cerebrospinal fluid
CT	Computed tomography
CTV	Clinical target volume
DS-GPA	Diagnosis-specific Graded Prognostic Assessment
EORTC	European Organization for Research and Treatment of Cancer
FI	Functional independence
GPA	Graded Prognostic Assessment
GTV	Gross tumor volume
HSRS	Hypofractionated stereotactic radiosurgery
KPS	Karnofsky Performance Status
LC	Local control
LINAC	Linear accelerator
LMD	Leptomeningeal disease
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
OS	Overall survival
PTV	Planning target volume
QoL	Quality of life
RCT	Randomized controlled clinical trial
RN	Radiation necrosis
RPA	Recursive partitioning analysis
RTOG	Radiation Therapy Oncology Group
SRS	Stereotactic radiosurgery
UPMC	University of Pittsburgh Medical Center
WBRT	Whole-brain radiotherapy

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Introduction

Brain metastases account for the majority of intracranial brain tumors, most frequently originating from cutaneous melanoma and carcinomas of the lung, kidney, and breast. Brain metastases appear in 20–40% of cancer patients, even in the setting of controlled extracranial disease, leading to 200,000 newly diagnosed cases per year in the United States [1].

The prognosis of patients with brain metastases has evolved over time, with survivals historically ranging from 1 to 2 months for untreated patients to up to 27 months and beyond with multi-modal therapy. Whole-brain radiotherapy (WBRT) has been

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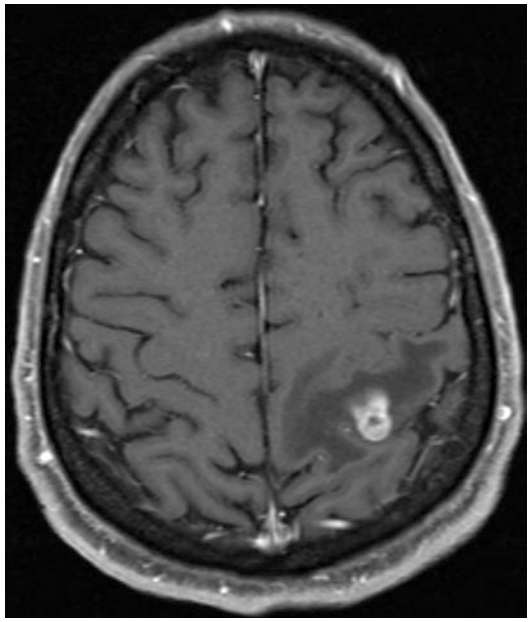

Fig. 22.1 Typical appearance of a T1-weighted post-contrast axial MRI image from a patient with a metastatic brain lesion from primary lung cancer located on the left postcentral gyrus with associated edema

utilized for more than 60 years and has shown a benefit in the treatment of neurologic symptoms and intracranial tumor control. However, in more recent years, WBRT has been shown to increase the risk of iatrogenic neurocognitive deficits and worsen quality of life (QoL) relative to stereotactic radiosurgery (SRS) [2]. Advancements in imaging technology have allowed for early (presymptomatic) identification of brain metastatic lesions in cancer patients (Fig. 22.1). As a result, SRS has become a dominant therapeutic option in the management of selected patients with one to four metastases and even in patients harboring 10 or more lesions [3].

Contemporary management of patients with brain metastases typically involves a multimodality regimen, including some combination of surgery, WBRT, SRS, glucocorticoids, and/or systemic therapy. Each patient should be evaluated in a personalized manner, and ideally, every patient eligible for treatment should also be considered for radiosurgery, weighing the risks and benefits [4, 5].

In this chapter, we will discuss the rationale for patient selection in SRS, SRS in the postoperative and preoperative setting, SRS for previously irradiated patients, and SRS near critical intracranial structures.

Stereotactic Radiosurgery

During SRS, a large dose of highly conformal radiation is delivered in one to five fractions at the targeted lesion. This is possible due to the creation of a sharp dose fall-off at the margin of the tumor that allows for the sparing of surrounding normal tissue. Since the Swedish neurosurgeon Lars Leksell described the stereotactic utilization of therapeutic irradiation in 1951 in the paper entitled "The Stereotaxic Method and Radiosurgery of the Brain" [6], newer systems have been launched allowing improved sparing of normal brain tissue. Currently, linear accelerator (LINAC)-based SRS, Cyberknife®, and Gamma Knife® technologies allow treating patients with "frameless" SRS with safety and reliability afforded by real-time patient tracking during irradiation.

SRS has emerged as one of the most effective treatments for the management of brain metastases. SRS has similar survival outcomes and is associated with less neurocognitive side effects, as compared to WBRT [2, 7]. Furthermore, it is often delivered in a single ambulatory session and does not interrupt or delay systemic therapies.

Prognostic Scoring Systems and Patient Selection

Patients with brain metastases were generally classified as a single group until 1997, when a paradigm shift occurred after the publication of the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) [8]. The RPA identified patient clinical factors

that influence survival and prognosis, allowing for improved clinical decision making. Later, specific biological tumor features were included in the Graded Prognostic Assessment (GPA) and diagnosis-specific GPA (DS-GPA) scoring systems [9, 10], incorporating more disease-specific parameters and even molecular profiles into the prognostic systems. Consequently, clinicians have more tools than ever to provide patients with optimized and personalized therapy.

Stereotactic Radiosurgery for the Management of Patients with One to Four Brain Metastases

Role of Surgical Resection

Phase III randomized clinical trials (RCT) have established that surgery improves the survival of oligometastatic intracranial disease [11–13]. Patchell et al. described the benefit of adding surgery to WBRT in patients with solitary brain metastasis, by randomizing patients into "surgery + WBRT" versus "biopsy only + WBRT"; surgery improved local control, preservation of functional status, and most importantly, overall survival (OS) [12]. To determine if surgery alone without WBRT was sufficient for patients presenting with solitary brain metastasis, Patchell et al. conducted a subsequent phase III RCT and found that surgery with WBRT was superior to surgery alone in terms of intracranial tumor control (local and distal failure) and decreasing neurologic death; however, there was no significant difference with regard to OS [14]. Very similar findings in oligometastatic patients presenting with one to three lesions were reported more than a decade later by Kocher et al. as part of the EORTC 22952-26001 study (Table 22.1) [15]. Thus, patients with oligometastatic disease should routinely receive neurosurgical evaluation for potential resection. This is especially important in patients with large tumors (generally >3 cm), particularly if it is causing edema and/or if neurologic symptoms refractory to steroid management, as surgical decompression is the fastest manner to improve neurological function [20, 21].

Postoperative Irradiation: SRS or WBRT?

Even as the studies from Patchell et al. [14] and Kocher et al. [15] positioned postoperative WBRT as the standard of care in oligometastatic patients, concerns were raised over the detrimental effects of WBRT on quality of life (QoL) domains such as fatigue and cognitive impairment [2, 19, 22, 23].

As a result of the most recent advances in SRS, radiosurgery has challenged the historical use of WBRT. Postoperative SRS to the surgical cavity following the resection of brain metastases has established itself as a reasonable standard of care, owing to data from phase III RCT [24]. The parallel development of hypofractionated postoperative SRS and preoperative SRS could potentially both minimize symptomatic radiation-induced injury and improve local tumor control [25–27].

Postoperative Resection Cavity SRS

Apart from the neurotoxicity associated with WBRT, postoperative WBRT can delay systemic therapy, especially if the patient needs to recover from acute side effects.

Although numerous retrospective studies reported local control rates from 70% to 90% with SRS to the postoperative resection cavity [28], Brennan et al. from Memorial Sloan Kettering Cancer Center published the first prospective trial and detailed local control, distant failure, and overall survival for patients with limited number of metastases. Delivering a median margin dose of 18 Gy (15–22 Gy), approximately 85% local control was reported during a median follow-up of 12 months [29].

Two recent phase III RCTs further validated the role of adjuvant postoperative SRS after

Table 22.1 Randomized controlled clinical trials evaluating different treatment combinations for patients carrying limited brain metastases

Phase III randomized controlled trials evaluating the role of surgery, SRS, and WBRT through the time									
Study	Randomization		Criteria	Primary end point	Tumor control		Survival	Functional outcomes	Radiation necrosis
					Local control	Distal control			
Evaluating the addition of surgery to WBRT									
Patchell et al. (1990) [12]	WBRT + Surgery	($n = 25$)	1 lesion	NR	52%	20%	40 w	Sx > Bx	NR
	WBRT + Biopsy	($n = 23$)	No RT		20% ($p < 0.02$)	13% ($p = 0.52$)	15 w ($p < 0.01$)	($p < 0.005$)	
Vetch et al. (1993) [11]	WBRT + Surgery	($n = 32$)	1 lesion	Overall survival	NR	NR	10 m	Sx + WBRT>	NR
	WBRT	($n = 31$)					6 m ($p < 0.04$)*	WBRT ($p < 0.06$)	
Mintz et al. (1996) [13]	WBRT + Surgery	($n = 41$)	1 lesion	Overall survival	NR	NR	6.3 m	NS	NR
	WBRT	($n = 43$)					5.6 m ($p = 0.24$)		
Evaluating the addition of WBRT to surgery									
Patchell et al. (1998) [14]	Surgery + WBRT	($n = 49$)	1 lesion	Local control	90%	86%	NS	NS	NR
	Surgery	($n = 46$)			54% ($p < 0.01$)	37% ($p < 0.01$			
Kocher et al. (2011)[a] [15]	Surgery + WBRT	($n = 81$)	1–3 lesions	OS with FI	59%	42%	10.7	NS	NR
	Surgery	($n = 79$)			27% ($p < 0.001$)	23% ($p < 0.008$)	10.9 ($p = 0.89$)		
Evaluating the addition of SRS to WBRT									
Kondziolka et al. (1999) [16]	WBRT + SRS	($n = 13$)	2–4 lesions	Local control	92%	34 m**	11 m	NR	0%
	WBRT	($n = 14$)	<2.5 cm		0% ($p < 0.001$)	5 m ($p < 0.002$)	7.5 m ($p < 0.22$)		0%
Andrews et al. (2004) [17]	WBRT + SRS	($n = 164$)	1–3 lesions	Overall survival	82%	NR	6.5 m	WBRT + SRS >	
	WBRT	($n = 167$)	<4 cm		71% ($p = 0.01$)	NR	4.9 m ($p = 0.04$)***	WBRT ($p = 0.03$)	

Evaluating the addition of WBRT to SRS									
Aoyama et al. (2006) [18]	SRS + WBRT	(n = 65)	1–4 lesions	Overall survival	96.9%	67.6%	7.5 m	33.9%	4.6%
	SRS	(n = 67)	each <3 cm		91.0% (p = 0.02)	49.2% (p < 0.003)	8 m (p = 0.42)	26.9% (p = 0.53)	1.5%
Kocher et al. (2011)[b] [15]	SRS + WBRT	(n = 99)	1–3 lesions	OS with FI	81%	67%	10.7	NS	13%
	SRS	(n = 100)			69% (p = 0.04)	52% (p < 0.02)	10.9 (p = 0.89)		8%
Chang et al. (2009) [19]	SRS + WBRT	(n = 28)	1–3 lesions	Cognitive outcomes	100%	73%	63%	52%****	
	SRS	(n = 30)			67% (p = 0.012)	45% (p = 0.02)	21% (p < 0.003)	24%	
Brown et al. (2016) [2]	SRS + WBRT	(n = 102)	1–3 lesions	Cognitive outcomes	90%	92.3%	7.4 m	SRS > WBRT+SRS	2.9%
	SRS	(n = 111)	<3 cm		73% (p < 0.003)	69.9% (p < 0.001)	10.4 m (p = 0.92)	For CP and QoL	4.5% (p = 0.72)

Abbreviations: *WBRT* whole-brain radiation therapy, *SRS* stereotactic radiosurgery, *Sx* surgery, *NR* not reported, *NS* not significant, *LC* local control, *OS* overall survival, *FI* functional independence, *CP* cognitive preservation

∗No differences for patients with active extracranial disease. ∗∗Time to any brain failure. ∗∗∗Survival time for patients with single metastasis (months). ∗∗∗∗HVLT-R total recall mean probability to decline

a & b are part of the same RCT (EORTC 22952-26001)

surgical resection of a limited number of metastases. Mahajan et al. [30] randomized 132 patients with one to three lesions to receive surgery and SRS or surgery alone, with respective local tumor control rates of 72% and 42%, supporting the use of SRS in the postoperative setting. Brown et al. reported results of NCCTG (N107C/CEC3) [31], a cooperative group phase III RCT comparing surgery + SRS versus surgery + WBRT in 194 patients with resected single metastatic brain lesions. Cognitive deterioration at 6 months was less frequent with SRS than with WBRT. As no differences were found in overall survival during a median 11.1 months follow-up, SRS was recommended over WBRT as a less toxic alternative in these patients (Table 22.2).

Larger tumor size/volume has been reported as an unfavorable risk factor for local control [32–34]. Brennan et al. had reported that tumor diameter >3 cm as well as superficial dural/pial invasion were associated with increased local failure [29]. On the other hand, lesions <3 cm, deep lesions, and non-small cell lung cancer (NSCLC) histology were associated with improved local control in the same study. In general, tumor recurrence at the surgical site was associated with increased volume of the surgical cavity or the lack of a 1–3 mm margin.

The Radiation Therapy Oncology Group 95-08 trial established the initial SRS margin dose recommendations in recurrent brain metastases and gliomas based on tumor diameter. However, it is now clear that dose prescription for SRS to a resection bed will depend on the postoperative resection cavity volume on postoperative imaging, as well as tumor location, previous irradiation, and prescription isodose.

The role of the margin expansion in target delineation was initially studied by the Stanford group. Soltys et al. [35] found improved local control in treatment plans with a lower conformality index—a measure of the compactness of the high-dose radiation given during SRS relative to the target volume. Choi et al. [36] later prospectively studied the role of target margin on tumor control of resection cavities treated by SRS, finding that the addition of 2 mm margins contributed to a statistically significant reduction in local failure at 12 months (16% vs 3%), with no significant increase in toxicity. The use of margin expansions is heavily dependent on radiosurgical platform and technique; extrapolation between centers should be done with caution.

Soliman et al. [37] published the *Contouring Consensus Guidelines for Postoperative Completely Resected Cavity Stereotactic Radiosurgery for Brain Metastases* in 2017, where SRS experts contoured 10 postoperative resection cavities of brain metastasis patients with lesions located in either supratentorial or infratentorial regions. Overall, the absolute kappa agreement for clinical target volume (CTV) was high in each of the cases (mean sensitivity 0.75, mean specificity 0.98). The findings led to the following recommendations on CTV contouring: (1) CTV should include the entire contrast-enhancing surgical cavity using the T1-weighted gadolinium-enhanced axial MRI scan, excluding any vasogenic edema determined by MRI; (2) CTV should include the entire surgical tract seen on postoperative CT or MRI; (3) if the tumor was in contact with the dura preoperatively, CTV should include a 5- to 10-mm margin along the bone flap beyond the initial region of preoperative tumor contact; (4) if the tumor was not in contact with the dura, CTV should include a margin of 1–5 mm along the bone flap; and (5) if the tumor was in contact with a venous sinus preoperatively, CTV should include a margin of 1–5 mm along the sinus. Clinical judgment is still required on a case-by-case basis until these recommendations are fully validated by clinical outcomes and patterns of recurrence [37].

Another important factor for postoperative SRS is the resection cavity volume dynamic [24]. Iorio-Morin et al. [38] recommended 3 weeks after resection as ideal timing to deliver SRS, after they found longer surgery-to-SRS delay to be associated with local recurrence on a multivariate analysis. This agrees with Patel et al. [39] who recommend against delaying SRS after surgery. After prospectively reviewing 79 cases, the authors found that there was a 28% increase in the postoperative cavity volume with a median time of surgery-to-SRS of 20 days and that, the

Table 22.2 Randomized clinical trials evaluating postoperative stereotactic radiosurgery to resection cavities in patients with brain metastases

Postoperative stereotactic radiosurgery to resection cavity in brain metastasis									
Study	Randomization		Criteria	Primary end point	Tumor control		Survival	Functional outcomes	Radiation necrosis
					Local control	Distal control			
Brennan et al. (2014)	Surgery + SRS	(n = 49)	1–2 lesions	LC at	85%	44%	14.7 m	NR	17.50%
Phase II [29] (MSKCC)			> 18 yo	12 m	50% (p = 0.08)[a]				
			PTV = cavity + 2 mm						
Mahajan et al. (2017)	Surgery + SRS	(n = 64)	1–3 lesions	LC	72%	42%	17 m	NR	0%
Phase III [30]	Surgery + Obs	(n = 68)	>3 yo		43% (p = 0.015)	33% (p = 0.35)	18 m (p = 0.24)		
			PTV = cavity + 1 mm						
Brown et al. (2017)	Surgery + SRS	(n = 98)	1 lesion, >18 yo	OS and	61%	64.70%	12.2	CDFS: 3.7 m	1%
Phase III [31]	Surgery + WBRT	(n = 96)	<5 cm	CDFS	81% (p < 0.0007)	89.2% (p < 0.0005)	11.6 (p = 0.7)	3 m (p < 0.001)	0%
			PTV = cavity + 2 mm						

Abbreviations: *WBRT* whole-brain radiation therapy, *SRS* stereotactic radiosurgery, *NR* not reported, *LC* local control, *OS* overall survival, *CDFS* cognitive deterioration free survival, *PTV* planning target volume, *Obs* observation

[a]Based on competing risk analysis including patients who completed postsurgical SRS and those who did not receive SRS (n = 40 and n = 10, respectively)

smaller the cavity, the higher the probability of postoperative cavity volume enlargement. The ideal interval between surgical resection and delivery of SRS was conjectured to be 2–3 weeks, as it allows for recovery after surgery and limits risk of local recurrence. Ultimately, though, it is clear that resection cavity sizes fluctuate after surgery. As such, it is imperative that planning MRIs be performed as close as possible to the actual time of radiation delivery. Platforms that involve MRI acquisition on the day of radiation treatment may thus have an inherent advantage in accuracy.

Hypofractionation and Postoperative Resection Cavity SRS

Single fraction SRS may have increased risk of toxicity in patients who have been previously irradiated, have lesions larger than 3 cm in diameter, produce more than 1 cm of midline shift, and/or abut critical organs-at-risk [40, 41]. According to the RTOG 90-05, recurrent previously irradiated lesions of 3.1–4.0 cm receiving 15 Gy, as the maximum tolerated dose, present a risk of unacceptable neurological toxicity up to 16 times that of lesions <2 cm [42].

Hypofractionated SRS is being increasingly used as it allows for dose escalation while limiting the risk profile, taking advantage of the improved repair of normal brain tissue. Eaton et al. reported on local control and the incidence and severity of radiation necrosis (RN) among patients treated with single fraction SRS or hypofractionated SRS (HSRS) for postoperative resection cavities ≥3 cm in diameter. Seventy-six patients with a median follow-up of 11 months were included. No significant differences in local control were found, but single-fraction SRS was associated with higher risk of radiation necrosis on multivariate analysis (HR: 3.81; 95% CI 1.04–13.93, $p = 0.043$).

Although several other retrospective studies support the utilization of hypofractionated SRS in the postsurgical setting for brain metastases [25, 26], there is still a lack of RCT data supporting the superiority of hypofractionated SRS over single-fraction SRS with regard to efficacy and toxicity.

Preoperative SRS

A novel potential strategy to approach some of the drawbacks associated with postoperative SRS is the use of preoperative SRS. Advantages include lack of need for margin addition to the gross tumor volume (GTV; GTV = PTV or planning target volume), no delay in treatment delivery, and the decreased risk of potential seeding of viable malignant cells into the CSF during surgery. Given that preoperative SRS treats a non-violated brain metastatic lesion, the borders will be well defined for target delineation; this could explain the decreased risk of radiation necrosis reported with this technique [25, 43].

Asher et al. [44] published the first study regarding local efficacy and safety of preoperative SRS for patients with one to three metastases where at least one of them was scheduled for surgical resection. A dose reduction strategy was used under the principle that intact brain metastases would maintain their blood supply and oxygenation and consequently a lower dose would be necessary to reach the same biological effect; 80% of the standard dose according to RTOG 95-08 was delivered 48 hours before surgery and no margins were applied for delineation (GTV = PTV). Overall survival at 6 and 12 months was 77.8% and 60% and local control at 6, 12, and 24 months was 97.8%, 85.6%, and 71.8%, respectively. There were no reports of leptomeningeal disease (LMD) during the 12-month follow-up.

A subsequent study from the same group compared postoperative WBRT with preoperative SRS. There were no differences in OS or LC, and interestingly no advantage with regard to LMD with WBRT [45].

Two potential drawbacks could arise with the use of preoperative SRS. The first is the possibility of incomplete resection of the metastatic lesion after a lower and less ideal preoperative radiosurgical dose. The second and major drawback is the lack of pathological confirmation of the lesion. Although there are no robust data, the

reported rate of false positive lesions ranges from 2% to 11%.

Radiosurgery as Definitive Treatment

SRS Versus Surgery

Currently, there are no clinical trials available comparing SRS and surgery. In 1996, Bindal et al. [46] from MD Anderson reported on this comparison. They prospectively followed 31 patients with lesions <3 cm who underwent SRS between 1991 and 1994 and matched them to 62 patients from a pool of retrospective cases that had only received surgery. Median SRS dose was 20 Gy (12–22 Gy) and WBRT was given equally in both groups. They found improved overall survival and local control with surgery. The authors suggested that SRS should be limited to surgically inaccessible lesions or patients with significant medical comorbidities.

Muacevic et al. [47] reported the results from a phase III RCT that was stopped prematurely given poor accrual. In the final analysis based on 64 patients with a single lesion <3 cm and randomized into surgery + WBRT or SRS alone, the authors found similar OS (median, 9.5 vs. 10.8 months, $p = 0.8$), LC (82% vs. 96%, $p = 0.06$), and neurological death rates (29% vs. 11%, $p = 0.3$). Although higher rates of distal recurrence were observed with SRS, this difference was not seen after salvage therapy.

A phase III RCT comparing surgery and SRS (both with adjuvant WBRT) was reported by Ross et al. [48]. Although there was a trend favoring SRS regarding OS (6.2 vs 2.8 months) and median failure free survival (3.1 vs. 1.7 months), the number of patients ($n = 21$) was too small to obtain any robust conclusions.

In general, either treatment should not exclude the other. We have already discussed the benefit of postoperative resection cavity SRS, and there is a growing body of knowledge on ways to balance the risks and benefits of these two approaches. Recent retrospective series showing the benefit of adding surgery to SRS support this premise [20, 21]. Regardless, it is clear that surgical resection, unlike SRS, can provide immediate intracranial decompression and pathologic confirmation.

The National Comprehensive Cancer Network (NCCN) recommends that surgery is followed by either WBRT or SRS for patients with one to three lesions and limited systemic disease. The choice between surgery and SRS depends on several factors such as size and location; a small, deep lesion should be treated with SRS at an experienced institution [49]. Surgery also can lead to almost immediate symptom relief as well as rapid discontinuation of glucocorticoid therapy.

SRS with or Without WBRT

Two RCT comparing WBRT with WBRT + SRS reported suboptimal local control with WBRT alone in patients with limited metastases [16, 17]. Four recent randomized studies evaluated SRS versus WBRT + SRS in patients with up to three to four metastases [2, 15, 18, 19] and reported the following conclusions: (1) adjuvant WBRT improves local and distal control; (2) adjuvant WBRT increases the risk of neurotoxicity, with consequent neurocognitive and quality-of-life decline; and (3) adjuvant WBRT does not improve survival over SRS alone (Table 22.1). This last conclusion has been challenged by retrospective studies. Wang et al. [50] who analyzed 15 years of experience from Columbia University Medical Center and a new secondary analysis of the JROSG 99-1RCT published by Aoyama et al. [51] have suggested that WBRT + SRS may improve OS in select patients with favorable prognoses. A secondary analysis of EORTC 22952-26001 did not find any survival advantage for WBRT relative to SRS in patients with limited systemic disease or favorable GPA scores [52]. The National Comprehensive Cancer Network (NCCN) recommends SRS plus WBRT (Level 1 evidence) or SRS alone (Level 2B evidence) for patients with a single brain metastasis, limited systemic disease, and good performance status.

The American Society for Radiation Oncology (ASTRO) [53] released a list of definitive recommendations as part of the *Choosing Wisely* campaign and recommended against routinely adding adjuvant WBRT to SRS for patients with limited brain metastases. The impact of WBRT on QoL and cognition should be taken into consideration, especially as salvage SRS or WBRT is always an option for dealing with future recurrences without worsening toxicity.

Stereotactic Radiosurgery for the Management of Patients with More Than Four Brain Metastases

Patients with a higher number of brain metastases should be managed with WBRT or SRS as primary treatment, unless at least one of the indications for surgery is present. While select patients with poor prognosis are offered WBRT [15], SRS is indicated for patients with good performance status and low overall tumor volume [49].

The group from University of Pittsburgh Medical Center (UPMC) [54] published outcomes of SRS for patients with four or more metastatic brain lesions. They found that cumulative tumor treatment volume was the most important prognostic factor for survival, supporting the use of the total volume of brain metastases rather than the number of lesions for treatment decision making. In their analysis, patients with a total treatment volume <7 cc and <7 brain metastases benefited the most from single SRS [55].

Yamamoto et al. [3] published the results of a non-inferiority trial in 2014 finding no differences in survival or treatment-related adverse events between the group of patients treated with SRS for 5–10 brain metastases and the group with 2–4 lesions (largest tumor <10 mL in volume and <3 cm in longest diameter, total cumulative volume ≤15 mL, KPS ≥70, SRS only treatment). This study supports the use of SRS for patients with five or more lesions; however, further prospective data are needed to validate other aspects of this treatment; recursive partitioning analyses could be useful to identify the groups of patients that can benefit the most from SRS. Several such studies are currently underway.

Stereotactic Radiosurgery in the Reirradiation Setting

Radiation necrosis is a known potential complication of SRS and can be difficult to distinguish clinically and/or radiographically from tumor recurrence. For intact brain metastases treated with SRS, rates of radiographic radiation necrosis (RN) could reach up to 24%, while in the postoperative resection cavity setting RN rates range from 1.5% to 18% [24]. If there is a high index of suspicion for recurrence, resection or stereotactic biopsy should be considered.

If recurrence is pathologically confirmed, SRS could be delivered as a salvage treatment in this context after previous WBRT. In the setting of resection for tumor recurrence after previous SRS, adjuvant therapy should be individualized, although observation after gross total resection is a reasonable approach. Repeat SRS can be offered, and other options include resection with intraoperative brachytherapy, detailed elsewhere in this book, and laser interstitial thermal therapy (LITT) to cauterize the tissue.

For patients who have previously been treated with SRS, the NCCN guidelines [49] recommend repeat SRS if there was a durable response longer than 6 months as long as imaging supports active tumoral lesion and not necrosis (2B recommendation). That said, imaging in the recurrent, post-treatment setting is often a mixed picture, and thus clinician best judgment must prevail. Because of the possibility of pseudoprogression in patients with metastatic disease, it is often prudent to monitor suspicious post-radiosurgical abnormalities unless they become symptomatic.

SRS for Brain Metastases Involving Eloquent or Critical Structures

Radiating eloquent regions of the brain requires a careful analysis of risk and benefit in order to prevent damage to adjacent tissues that serve important neurologic functions (Fig. 22.2). Sensorimotor, language, visual cortex, hypothalamus, thalamus, brainstem, cerebellar nuclei, optic pathways, and regions immediately adjacent to these structures are generally considered organs at risk of symptomatic radiation injury.

Two retrospective series evaluating SRS for metastases located in eloquent areas (primary motor, somatosensory, speech, and visual cortex; basal ganglia; thalamus; and brainstem) indicated that it is safe and effective [56, 57]. Hsu et al. reported no differences in the overall survival when compared to the cohort harboring non-eloquent lesions receiving a higher median prescription dose. New neurological deficits were transient and rates of radiation necrosis were as expected for SRS.

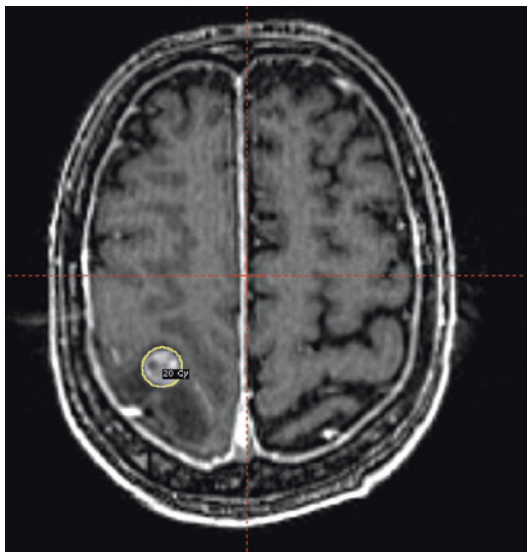

Fig. 22.2 T1-weighted post-contrast axial MRI image from a patient presenting a metastatic brain lesion from a soft tissue sarcoma primary located on the right postcentral gyrus. Given the tumor volume, SRS was delivered to a dose of 20 Gy. There have been no complications, and local control was maintained in the last follow-up at 12 months

In a study of radiosurgery in 161 patients harboring 189 metastases in the brainstem, 52% of had received whole brain radiotherapy (WBRT) prior to SRS. These results suggest that SRS can be safely administered after WBRT, even in eloquent or critical brain locations [58]. However, after this report, we conducted an international cooperative study to define response and toxicity in brainstem metastases and found an increased risk of injury when SRS is administered shortly after WBRT [40]. This could be due to sublethal damage from WBRT decreasing with time, allowing for recovery and lower radiation-induced injury risk with subsequent SRS. It is evident that previous intracranial therapies, specifically radiation, should be considered during treatment decision making.

Taken together, it is possible for an experienced team to perform stereotactic radiosurgery to brain metastases located within or near critical structures. In the presence of an intact tumor capsule, the target would consist solely of tumor cells (i.e., non-neural tissue), and therefore accurate delineation and accurate conformal delivery should rarely result in clinical toxicity. Furthermore, given the dismal prognosis of patients carrying metastatic brain lesions, it is possible that the survival is not long enough for late complications such as radiation necrosis to present.

Hypofractionation in SRS is advantageous for larger lesions, allowing maintenance of therapeutic dose while decreasing the risk of radionecrosis. Hypofractionated SRS delivery for lesions located in critical structures is a topic of ongoing prospective clinical research.

Conclusion

Stereotactic radiosurgery has proven safety and efficacy for the management of brain metastatic lesions in the definitive and adjuvant setting. The total volume of brain metastases, rather than the number of lesions, seems to be more important to clinical decision making. With the appropriate clinical and biological factors taken

into consideration, SRS is a powerful therapeutic tool that can improve the quality of life of our patients. Prospective data are needed to further validate the superiority of novel SRS approaches.

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