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Critical Review

Stereotactic Radiosurgery for Postoperative Metastatic Surgical Cavities: A Critical Review and International Stereotactic Radiosurgery Society (ISRS) Practice Guidelines

Kristin J. Redmond, MD, MPH,[*] Antonio A.F. De Salles, MD, PhD,[†] Laura Fariselli, MD,[‡] Marc Levivier, MD, PhD,[§,‖] Lijun Ma, PhD,[¶] Ian Paddick, MSc,[#] Bruce E. Pollock, MD,[**] Jean Regis, MD,[††] Jason Sheehan, MD, PhD,[‡‡] John Suh, MD,[§§] Shoji Yomo, MD,[‖‖] and Arjun Sahgal, MD[¶¶]

[*]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University, Baltimore, Maryland; [†]HCor Neuroscience Institute, Heart Hospital (HCor), São Paulo, São Paulo, Brazil; [‡]Department of Neurosurgery, Unit of Radiotherapy, Fondazione IRCCS Istituto Neurologico C Besta, Milano, Italy; [§]Neurosurgery Service and Gamma Knife Center Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [‖]Faculty of Biology and Medicine (FBM), University of Lausanne, Lausanne, Switzerland; [¶]Department of Radiation Oncology, University of California San Francisco, San Francisco, California; [#]Medical Physics Ltd, Queen Square Radiosurgery Centre, London, United Kingdom; [**]Department of Radiation Oncology and Department of Neurologic Surgery, Mayo Clinic School of Medicine, Rochester, Minnesota; [††]Aix-Marseille University, INSERM, UMR 1106, Timone University Hospital, Functional Neurosurgery and Radiosurgery Department, Marseille, France; [‡‡]Department of Neurosurgery, University of Virginia, Charlottesville, Virginia; [§§]Department of Radiation Oncology, Taussing Cancer Institute Cleveland Clinic, Cleveland, Ohio; [‖‖]Division of Radiation Oncology, Aizawa Comprehensive Cancer Center, Aizawa Hospital, Matsumoto, Japan; and [¶¶]Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Canada

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Corresponding author: Kristin J. Redmond, MD, MPH; E-mail: kjanson3@jhmi.edu

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Purpose: The purpose of this critical review is to summarize the literature specific to single-fraction stereotactic radiosurgery (SRS) and multiple-fraction stereotactic radiation therapy (SRT) for postoperative brain metastases resection cavities and to present practice recommendations on behalf of the ISRS.

Methods and Materials: The Medline and Embase databases were used to apply the Preferred Reporting Items for Systematic Reviews and Meta-Analyses approach to search for manuscripts reporting SRS/SRT outcomes for postoperative brain metastases tumor bed resection cavities with a search end date of July 20, 2018. Prospective studies, consensus guidelines, and retrospective series that included exclusively postoperative brain metastases and had at minimum 100 patients were considered eligible.

Results: The Embase search revealed 157 manuscripts, of which 77 were selected for full-text screening. PubMed yielded 55 manuscripts, of which 23 were selected for full text screening. We deemed 8 retrospective series, 1 phase 2 prospective study, 3 randomized controlled trials, and 1 consensus contouring paper appropriate for inclusion. The data suggest that SRS/SRT to surgical cavities with prescription doses of 30 to 50 Gy equivalent effective dose (EQD) 2_{10}, 50 to 70 Gy $EQD2_5$, and 70 to 90 $EQD2_2$ are associated with rates of local control ranging from 60.5% to 91% (median, 80.5%). Randomized data suggest improved local control with single-fraction SRS compared with observation and improved cognitive outcomes compared with whole-brain radiation therapy (WBRT). The toxicity of SRS/SRT in the postoperative setting was limited and is reviewed herein.

Conclusions: Although randomized data raise concern for poorer local control after resection cavity SRS than WBRT, these findings may be driven by factors such as conservative prescription doses used in the SRS arm. Retrospective studies suggest high rates of local control after single-fraction SRS and hypofractionated SRT for postoperative brain metastases. With a superior neurocognitive profile and no survival disadvantage to withholding WBRT, the ISRS recommends SRS as first-line treatment for eligible postoperative patients. Emerging data suggest that fractionated SRT may provide superior local control compared with single-fraction SRS, in particular, for large tumor cavity volumes/diameters and potentially for patients with a preoperative diameter greater than 2.5 cm.

Introduction

The first landmark study by Patchell et al,[1] reported in 1990, randomized patients with a solitary brain metastasis to whole-brain radiation therapy (WBRT) alone versus surgery followed by WBRT. They reported significant improvements in both local control (LC) and overall survival in patients who underwent surgery. The second landmark study by Patchell et al,[2] reported in 1998, randomized patients after surgery to observation versus adjuvant WBRT, and significant benefits were reported with respect to LC. As a result, for decades, surgery has been considered the standard of care in patients with solitary brain metastases, controlled extracranial disease, and excellent performance status.

In modern practice, single-fraction stereotactic radiosurgery (SRS) and multiple-fraction stereotactic radiation therapy (SRT) have emerged as non-invasive approaches to provide high rates of LC. Therefore, surgery is typically now reserved for patients with solitary metastases greater than 2 cm, hemorrhage, symptomatic mass effect or toxic edema, radioresistant histologies, or indications for a tissue diagnosis. After surgery, the standard of care had been adjuvant WBRT based on the discussed historic randomized trials, but recently this has been challenged with the application of SRS and SRT to the surgical bed. Although early adopters began treating surgical cavities with either a single-fraction SRS or up to 5 fractions of SRT, it was not until 2018 that dedicated randomized trials were reported.

The purpose of this systematic review was to summarize the current literature specific to SRS and SRT for postoperative brain metastases resection cavities and to provide recommendations for treatment on behalf of the International Stereotactic Radiosurgery Society (ISRS) Guidelines Committee.

Methods and Materials

A systematic review of the literature was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach.[3]

Search strategy

The Medline and Embase databases were used to search for manuscripts reporting outcomes after SRS and SRT for postoperative brain metastases tumor bed resection cavities with a search end date of July 20, 2018. Search words included the following: "postoperative stereotactic radiosurgery (SRS)," "resection cavity SRS," "fractionated stereotactic radiosurgery for resected brain metastases," "Gamma Knife for postoperative brain metastases," and "Cyberknife for postoperative brain metastases."

Prospective studies, consensus guidelines, and retrospective series that included exclusively postoperative brain metastases, had at minimum 100 patients, and were published in manuscript form in journals written in English were considered eligible.

Outcome measures

The primary outcome measure was the rate of LC. In addition, data regarding tumor histology, technique, planning target volume (PTV) margin, median follow-up time, prior WBRT, the rate of distant brain parenchymal

failure, the rate of development of leptomeningeal disease, overall survival, prescription dose and number of fractions, rate of radionecrosis, and other late toxicities were also recorded.

Equivalent effective dose

The outcomes of variable dose and fractionation schedules were compared by calculation of the equivalent effective dose in 2 Gy fractions using an alpha/beta (α/β) of n ($EQD2_n$), using the following formula: $EQDX_{\alpha/\beta} = D \cdot \frac{d+\alpha/\beta}{X+\alpha/\beta}$, where X is the reference fraction size, defined in this manuscript as 2 Gy, d is the absorbed dose per fraction for the reference treatment plan, and D is the total absorbed dose in the reference treatment plan.[4] The α/β ratio was calculated for 3 values (α/β of 2, 5, and 10) to represent a range of plausible α/β, as suggested by van Leeuwen et al.[5]

Results

The details of the PRISMA search are shown in Figure 1. Primary database screening identified a total of 212 candidate citations (157 from Embase and 55 from PubMed). After removal of duplicates, retrospective series with <100 patients, and manuscripts written in a language other than English, a total of 100 manuscripts were selected for full-text screening. Further review was used to remove abstracts, manuscripts that reported outcomes for both intact brain metastases and resection cavities, and those that were not focused on SRS/SRT. In the end, a total of 13 manuscripts were deemed acceptable for inclusion. These included 8 retrospective series, 1 phase 2 prospective trial, 3 randomized controlled trials, and 1 consensus contouring paper.

Patient and target characteristics

Three randomized controlled trials including exclusively radiation-naïve patients were deemed notable studies[6-8] and are summarized in Table 1. A total of 1248 tumor beds in 1187 patients were included in the retrospective and single-arm phase 2 clinical trials.[9-17] The specifics of the selected studies, as well as other pertinent information, are listed in Table 2. Six of them excluded patients receiving WBRT and 1 study did not report these data. Three of the retrospective studies allowed patients with prior WBRT and had a median of 15% of patients who received it (range, 3%-39.2%). Prescription radiation doses are summarized in Table 3 but generally ranged from 30 to 50 Gy $EQD2_{10}$, 50 to 70 $EQD2_5$, and 70 to 90 $EQD2_2$ delivered in 1 to 5 fractions. Six studies used exclusively linear accelerator (LINAC)-based systems, 2 exclusively used Gamma Knife, and 1 exclusively used a robotic platform. The remainder used a mix of technologies.

Tumor control outcomes

Overall, prescription doses in the range of 30 to 50 Gy $EQD2_{10}$, 50 to 70 $EQD2_5$, and 70 to 90 $EQD2_2$ are associated with acceptable rates of LC, but formal comparative studies are warranted to evaluate both tumor control and toxicity outcomes between regimens.

Figure 2 shows tumor control outcomes for both the retrospective and prospective series included in this manuscript. Across all of the series, the median LC of the tumor bed resection cavity (Fig. 2A) was 80.5% (range, 60.5%-91%).

Level I data demonstrate that postoperative single-fraction SRS is associated with better LC than observation after

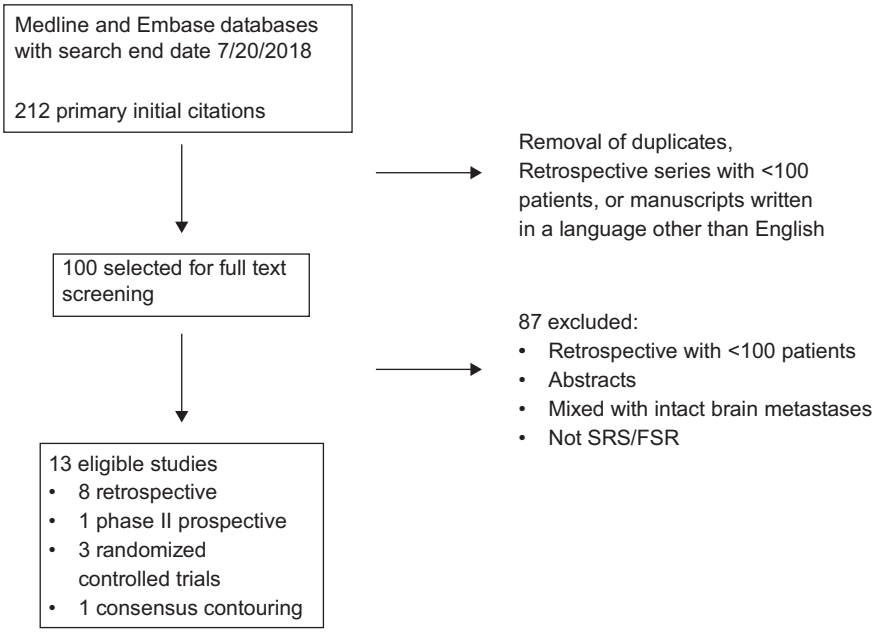

Fig. 1. Summary of PRISMA search. *Abbreviations:* FSR = fractionated stereotactic radiotherapy; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SRS = stereotactic radiosurgery.

Table 1 Data summary of the randomized controlled studies

Study	Arms	N	Histology	Median prescription dose (Gy)/ fractions	Cognitive deterioration at 6 months	2-y cognitive failure	Margin to PTV	Median FU, mo	Local control	12-mo local control	Distant brain parenchymal failure	LMD	Median overall survival	Rate of radionecrosis
Brown et al, *Lancet Oncol,* 2017[6]	SRS	98	NR	12-20 Gy/1 fraction	52%	NR	2 mm	11.1	60.5% (12 mo)	60.50%	35.50%	7.20%	12.2 mo	NR
	WBRT	96	NR	30 Gy/10 fractions or 37.5 Gy/15 fractions	85%	NR	NA		80.6% (12 mo)	80.60%	10.80%	5.40%	11.6 mo	NR
Kepka et al, *Radiother Oncol,* 2016[8]	SRS	29	Lung (48%) Colorectal (24%) Breast (3.5%) Melanoma (3.5%) Kidney (7%) Other (14%)	15 Gy /1 fraction or 25 Gy/5 fractions	NR	75%	3 mm	29	74%	NR	NR	1*	NR	NR
	WBRT	30	Lung (50%) Colorectal (6.5%) Breast (20%) Melanoma (10%) Other (13.5%)	30 Gy/10 fractions	NR	62%	NA		75%	NR	NR	1*	NR	NR
Mahajan et al, *Lancet Oncol*, 2017[7]	SRS	64	Melanoma (22%) Lung (21%) Breast (14%) Other (43%)	16/1	NR	NR	1 mm	11.1	76%	72%	68%	18.75%	7.5 mo	0
	Obs	68	Melanoma (20%) Lung (20%) Breast (22%) Other (38%)	NA	NR	NR	NA		52%	43%	77%	11.76%	5.4 mo	0

Abbreviations: FU = follow-up; LMD = leptomeningeal disease; mo = month; NA = not applicable; NR = not reported; obs = observation; PTV = planning target volume; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

Local control was cumulative unless otherwise stated. Total intracranial control included both the tumor bed and/or distant sites of the brain.

* Overall in the study, 1 patient was reported to develop LMD but the arm was not stated.

Table 2 Data summary of the retrospective and phase 2 studies

Author and year	Data type	Tumor bed/ patients treated	Cancer Histology	Technique	Margin to PTV	Prior WBRT	Median FU, mo	Local control	Rate of distant brain parenchymal failure	Rate of LMD/median time to LMD, mo	Median overall survival	Median prescription dose (Gy)/no. of fractions	$EQD2_{10}$	Rate of radionecrosis
Atalar et al, *Int J Radiat Oncol Biol Phys*, 2013[9]	Retrospective	175/165	NSCLC 76 (43%) Breast 27 (15%) Melanoma 24 (14%) Colon 18 (10%) GYN 6 (3%) Other 24 (14%)	CyberKnife	0-2 mm	0	12.4	87%	54%	13%/ 5 mo	17 mo	Dose according to RTOG 9005 and physician preference with multisession treatments predominantly for larger cavities	NR	NR
Combs et al, *Cancer Med*, 2018[11]	Retrospective	208/181	NSCLC (36.5%) Gastrointestinal cancer (15.5%) Breast (16%) Malignant melanoma (11%) RCC (2.8%) Sarcoma (1.1%) Others (17.1%)	LINAC	3-4 mm	3%	12.6	80.5%	63%	NR	16 mo	Munich 35/7*	Munich 49.6 Gy†	4%
Brennan et al, *Int J Radiat Oncol Biol Phys*, 2014[10]	phase 2	40/39	NSCLC (57%) Breast (18%) GI (8%) Melanoma (8%) Other (4%)	LINAC	2 mm	0	12	85% at 1 y	44% at 1 y	NR	14.7 mo	18/1	42 Gy	17.5%
Gui et al, *Pract Radiat Oncol,* 2018[12]	Retrospective	185/173	Lung (42%) Melanoma (14%) Breast (13%) RCC (10%) Sarcoma (4%) Head and neck (3%) Endometrial (3%) Ovarian (2%) Colorectal (2%) Other (6%)	CyberKnife 86% LINAC 14%	2 mm	NR	8.4	89.6%	NR	NR	NR	21/3	29.8 Gy	NR
Iorio-Morin et al, *J Neurosurg*, 2014[13]	Retrospective	113/110	NSCLC (50%) Breast (13%) Colorectal (12%) Melanoma (10%) Renal (5%) Other (10%)	Gamma Knife	1 mm	15%	10	75%	54%	11%	11 mo	18/1	42 Gy	22% but only 1 pathologically proven
Keller et al, *Int J Radiat Oncol Biol Phys*, 2017[14]	Retrospective	189/181	NSCLC (45.3%) Breast (11.1%) GI (9.9%) RCC (9.9%) Melanoma (8.8%) Ovarian (1.7%) GYN (2.8%) Unspecified (2.8%) Other (7.7%)	LINAC	2 mm	0	12	86.5% (2 y)	47.6% (2 y)	14%/ 3.8 mo	17 mo	33/3	57.8 Gy	18.5%
Luther et al, *Neurosurgery,* 2013[15]	Retrospective	120/120	NSCLC (40%) Breast (20.8%) Melanoma (15.8%) Unspecified (23.4%)	Gamma Knife	0	39.2%	8	85.8%	40%	NR	NR	16/1	34.7 Gy	NR
Minniti et al, *Int J Radiat Oncol Biol Phys*, 2013[16]	Retrospective	101/101	NSCLC (22.8%) Breast (18.8%) Colon (5.9%)	LINAC	2 mm	0	16	91%	53.5%	NR	17 mo	27/3	42.8 Gy	9%

(*Continued*)

Table 2 (*Continued*)

Author and year	Data type	Tumor bed/ patients treated	Cancer Histology	Technique	Margin to PTV	Prior WBRT	Median FU, mo	Local control	Rate of distant brain parenchymal failure	Rate of LMD/median time to LMD, mo	Median overall survival	Median prescription dose (Gy)/no. of fractions	$EQD2_{10}$	Rate of radionecrosis
Zhong et al, *Pract Radiat Oncol*, 2017[17]	Retrospective	27/27; >4 cm	Melanoma (27.8%) RCC (17.8%) Other (6.9%) NSCLC (41%) Breast (19%) Melanoma (22%) RCC (11%) Other (7%)	LINAC	2-3 mm	0	24	74% (estimated from Figure 1)	64.5% (2 y)	19.8% (at 2 y)	67.6% (1 y)	20/1 (median doses do not match stated BED)	50 Gy	28.4% (1 y)
Zhong et al, *Pract Radiat Oncol*, 2017[17]	Retrospective	90/90; ≤4 cm	NSCLC (46%) Breast (19%) Melanoma (20%) RCC (6%) GI (1%) Other (9%)	LINAC	2-3 mm	0	24	80% (estimated from Fig. 1)	56.6% (2 y)	22.8% (at 2 y)	80.6% (1 y)	18/1	42 Gy	26.9% (1 y)

Abbreviations: BED = biologically equivalent dose; $EQD2_{10}$ = equivalent effective dose in 2 Gy fractions using an α/β ratio of 10 Gy; FU = follow-up; GI = gastrointestinal; GYN = gynecologic; LINAC = linear accelerator; LMD = leptomeningeal disease; mo = month; mm = millimeter; NR = not reported; NSCLC = non-small cell lung cancer; PTV = planning target volume; RCC = renal cell carcinoma; RTOG = Radiation Therapy Oncology Group; WBRT = whole-brain radiation therapy; y = year.

Local control was cumulative unless otherwise stated.

* Freiburg 35/7 if recurrent/residual disease, 30/6 if gross total resection.

† Freiburg 52.5 Gy if recurrent/residual disease, 45 Gy if gross total resection.

surgical resection of brain metastases. Specifically, Mahajan et al[7] randomized 132 patients to either observation or single-fraction SRS after surgery. They report a 12-month LC of 43% in the observation arm and 73% in the SRS arm (P = .015). Equally importantly, there was no difference in overall survival between these 2 groups.

A recent randomized study demonstrated a 1-year LC of 61% after postoperative SRS, compared with 81% in patients receiving WBRT.[6] Importantly, there was no difference in overall survival between the 2 arms, with a median survival in both arms of approximately 12 months. Although the reason for this outcome remains unclear, it is possible that the conservative prescription radiation doses as low as 12 to 14 Gy in a single fraction delivered to larger cavities may have contributed; the biologically equivalent dose of 12 to 14 Gy in a single fraction is lower than those prescribed in the WBRT arm, in which patients received 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. Furthermore, the study used response evaluation criteria in solid tumors (RECIST) criteria to assess response, in which SRS-induced pseudoprogression might have been incorrectly categorized as true progression.

Furthermore, these randomized phase 3 trials suggest a relationship between tumor volume and LC. Specifically, Mahajan et al[7] reported 12-month freedom from local recurrence was 91% for patient with tumors less than 2.5 cm preoperatively, but fell to 40% to 46% in larger tumors. These data suggest that single-fraction SRS is associated with excellent LC for small resection cavities. However, given the poor LC associated with larger resection cavities, application of fractionated regimens may be more appropriate in patients with preoperative tumors larger than 2.5 cm. These data are supported by retrospective series, including that published by Minniti et al,[16] which demonstrated 1- and 2-year LC rates of 93% and 84%, respectively, for large resection cavities measuring greater than 3 cm when treated with the fractionated regimen of 27 Gy in 3 fractions. Similarly, a recent tumor control probability analysis confirmed higher recurrence rates after SRS/SRT for resection cavities with PTVs greater than 12 to 17 cm^3, but with a strong dose response.[18] Given that the maximum tolerated single-fraction doses to tumors 2−3 cm in diameter and greater than 3 cm in diameter have been previously estimated as 18 Gy and 15 Gy in 1 fraction, respectively,[19] these data suggest that fractionated SRT regimens may be necessary to safely deliver higher biologically effective doses in large resection cavities. In this light, Soliman et al[20] report a 1-year LC rate of 84% after 5-fraction hypofractionated SRT to resection cavities with a median prescription dose of 30 Gy (range, 25-35 Gy) in a cohort of patients of whom 57% had preoperative tumor sizes greater than 3 cm.

Distant brain failure and leptomeningeal dissemination

An important consideration when selecting patients for focal treatment with SRS/SRT rather than WBRT is the risk of

Table 3 Prescription radiation doses for the retrospective and phase 2 studies

Author, journal, year	Median total dose (Gy)/number of fractions	Median $EQD2_{10}$	Median $EQD2_5$	Median $EQD2_2$
Brennan et al, *Int J Radiat Oncol Biol Phys,* 2014[10]	18/1	42	59.1	90
Brown et al, *Lancet Oncol,* 2017[6]	12-20/1	22-50	29.1-71.4	42-110
Combs et al, *Cancer Med,* 2018[11]	35/7*	49.6	60	78.8
Gui, *Pract Radiat Oncol,* 2018[12]	21/3	29.8	36	47.3
Iorio-Morin et al, *J Neurosurg,* 2014[13]	18/1	42	59.1	90
Keller et al, *Int J Radiat Oncol Biol Phys,* 2017[14]	33/3	57.8	75.4	107.2
Kepka et al, *Radiother Oncol,* 2016[8]	15/1 or 25/5	31.3 or 31.25	42.9 or 35.7	63.8 or 43.8
Luther et al, *Neurosurgery,* 2013[15]	16/1	34.7	48	72
Mahajan et al, *Lancet Oncol,* 2017[7]	16/1	34.7	48	72
Minniti et al, *Int J Radiat Oncol Biol Phys,* 2013[16]	27/3	42.8	54	74.3
Zhong et al, *Pract Radiat Oncol,* 2017 (size >4 cm)[17]	20/1	50†	71.4	110
Zhong et al, *Pract Radiat Oncol,* 2017 (size ≤4 cm)[17]	18/1	42	59.1	90

Abbreviation: $EQD2_n$ = the equivalent effective dose in 2 Gy fractions using an α/β of n; Gy =gray.
* In Freiburg 35 Gy/7 was used if recurrent/residual disease, 30 Gy/6 if gross total resection.
† BED10 stated in the manuscript does not match the stated dose/fractionation. $EQD2_n$ calculations were based on the stated prescription.

development of new brain metastases. The median percentage of patients who received SRS that experienced distant brain parenchymal failure across all of the studies was 54% (range, 35.5%-68%; Fig. 2B). Randomized data did confirm higher rates of new brain metastases in patients receiving SRS compared with WBRT (35.5% vs 10.8%, respectively).[6] Nonetheless, the lack of a survival benefit of WBRT suggests that patients can be successfully salvaged without adversely affecting their long-term cancer outcome, suggesting that delaying or avoiding WBRT to preserve neurocognitive function for as long as possible is reasonable.

Another major concern regarding SRS for postoperative resection cavities is the risk of leptomeningeal failure, given that surgical manipulation may cause seeding. The median percent of patients who developed leptomeningeal disease (LMD) after SRS/SRT (Fig. 2C) was 14% (range, 7.2%-22.8%), which is higher than typically seen in series summarizing outcomes after SRS for intact metastases. However, randomized data did not demonstrate a higher risk of leptomeningeal failure in patients receiving SRS compared with WBRT (7.2% vs 5.4%, respectively).[6] It is unclear whether this may be related to variations in surgical technique, follow-up imaging specifications, and/or the definition of LMD used across studies, but methods to reduce this risk and salvage patients who develop LMD after SRS to resection cavities warrant further investigation and will be reviewed in the Discussion section.

Neurocognitive outcomes

Brown et al[6] randomized 194 patients to either single-fraction SRS or WBRT and found that the 6-month rate of cognitive deterioration was 52% after SRS and 85% after WBRT (P = .0003). Furthermore, there was once again no difference in overall survival between the groups. This study suggests that patients receiving SRS have better preservation of cognitive function than those receiving WBRT.

Nonetheless, it is important to note that the results of the Brown et al[6] study differ from those reported in the smaller randomized controlled study published by Kepka et al[8] the year prior, which reported 2-year incidences of neurologic failure of 75% after SRS and 62% after WBRT, as well as cumulative incidences of neurologic death of 66% after SRS and 31% after WBRT. One hypothesis for these seemingly conflicting findings is that the Kepka et al[8] study enrolled only 59 patients and therefore was underpowered to detect noninferiority of SRS as it was intended. Furthermore, the potential LC benefit of SRS would be from dose escalation, but the biological effectiveness of 30 Gy in 10 fractions delivered in the WBRT arm is comparable to the 15 Gy in 1 fraction or 25 Gy in 5 fractions delivered in the SRS/SRT arm in this study. Therefore, it is possible that the detriment in neurologic failure and higher risk of neurologic death in the SRS dose may have been driven at least in part by smaller target volumes receiving insufficient dose. In addition, data regarding tumor size were not reported for the 2 study arms, but we have now learned that preoperative tumor size is an important driver of LC, as discussed in the "Tumor control outcomes" section.[7]

Other toxicity

Figure 3 shows the rate of radionecrosis for all of the studies in which it was reported. Radionecrosis was defined

Table 4 ISRS summary recommendations

Recommendation	Level of evidence
After surgery for a brain metastasis, postoperative SRS is preferred over observation due to superior local control	I
For patients with 1 resected brain metastasis, ECOG performance status of 0-2, and a resection cavity measuring <5 cm, postoperative SRS to the resection cavity is recommended to minimize cognitive toxicity compared with whole brain radiation therapy	I
Target volume should include the resection cavity and entire surgical tract with consideration to expand the clinical target volume to include a 5-10 mm expansion beyond the preoperative tumor location along bone flap in those tumors contacting the dura preoperatively, while respecting anatomic barriers, and a 1-5 mm expansion along sinuses for tumors contacting a sinus preoperatively. In addition, a 2-3 mm radial expansion to PTV should be considered.	III
Prescription doses of approximately 30-50 Gy $EQD2_{10}$, 50-70 $EQD2_5$, and 70-90 $EQD2_2$, have been associated with reasonable local control, but formal comparative studies are warranted. Emerging data suggest single-fraction treatment without dose de-escalation is appropriate in cavities <2 cm in size and that fractionated regimens may provide superior local control compared with single-fraction SRS in patients with large metastases greater than 2.5-3 cm.	III
The consent process for brain metastases surgery should include a discussion of the risk of surgical dissemination of tumor manifesting as leptomeningeal disease.	III

Abbreviations: ECOG = Eastern Cooperative Oncology Group; $EQD2_n$ = the equivalent effective dose in 2 Gy fractions using an α/β of n; ISRS = International Stereotactic Radiosurgery Society; PTV = planning target volume; SRS = stereotactic radiosurgery.

variably across studies but most commonly was not graded, included both symptomatic and asymptomatic cases, and was a radiographic diagnosis rather than pathologically confirmed. It was reported in a median of 19% of patients (range, 0%-28%). Other late toxicity was reported in only 2 of the randomized studies and 1 retrospective study, but included cognitive disturbance in 3% to 5%, hearing impairment in 3% to 9%, seizure in 3%, and steroid dependency lasting greater than 4 months in 3%.

Target delineation

A single consensus contouring manuscript has been published.[21] The recommendation is that the clinical target volume (CTV) should include the entire contrast-enhancing surgical cavity, as well as the surgical tract, based on the postoperative T1 postgadolinium weighted magnetic resonance imaging (MRI). The authors recommend that tumors with preoperative involvement of the dura include a 5- to 10-mm margin beyond the preoperative region of tumor involvement, whereas tumors that did not contact the dura or contacted a venous sinus should include a 1- to 5-mm margin along the bone flap or sinus. In terms of the margin for the PTV expansion, the majority of studies included in this manuscript used a 2- to 3-mm radial expansion. However, additional data are needed regarding the association between margin size and tumor control probability and radionecrosis. It is also important to note that these recommendations represent expert opinion. They are supported by a recent pattern of failure analysis that found that the tumor volume contacted the dura in 100% of cavities that ultimately developed local recurrence, but only 67% of those were controlled after treatment.[22] Nonetheless, additional formal patterns of failure analyses will be essential to validate these suggestions.

Discussion

In this systematic review, we review the results of 13 manuscripts including a total of 1439 tumor beds in 1378 patients treated with surgery followed by postoperative SRS and SRT. Based on this comprehensive compilation of data, ISRS summary recommendations are shown in Table 4. Overall, these studies suggest reasonable rates of LC of approximately 80% with an acceptable risk of radionecrosis of less than 20%. Only 3 studies clarified the percentage of radionecrosis that wassymptomatic, which accounted for a median of 34% of the reported radionecrosis cases (range, 20%-65%).[14,16,17] The prescription doses used in this study are variable but, in aggregate, suggest that prescriptions ranging from 30 to 50 Gy $EQD2_{10}$, 50 to 70 $EQD2_5$, and 70 to 90 $EQD2_2$ are associated with satisfactory outcomes. The largest retrospective series published to date was outside of the data collection period of this review and similarly demonstrated excellent LC after delivery of similar dose/fraction schedules. The 12-month local failure rate was only 7%, with 8.9% and 5.5% of patients experiencing adverse radiation effects and symptomatic adverse radiation effects, respectively.[23]

Importantly, no studies to date have demonstrated a survival advantage of postoperative WBRT compared with

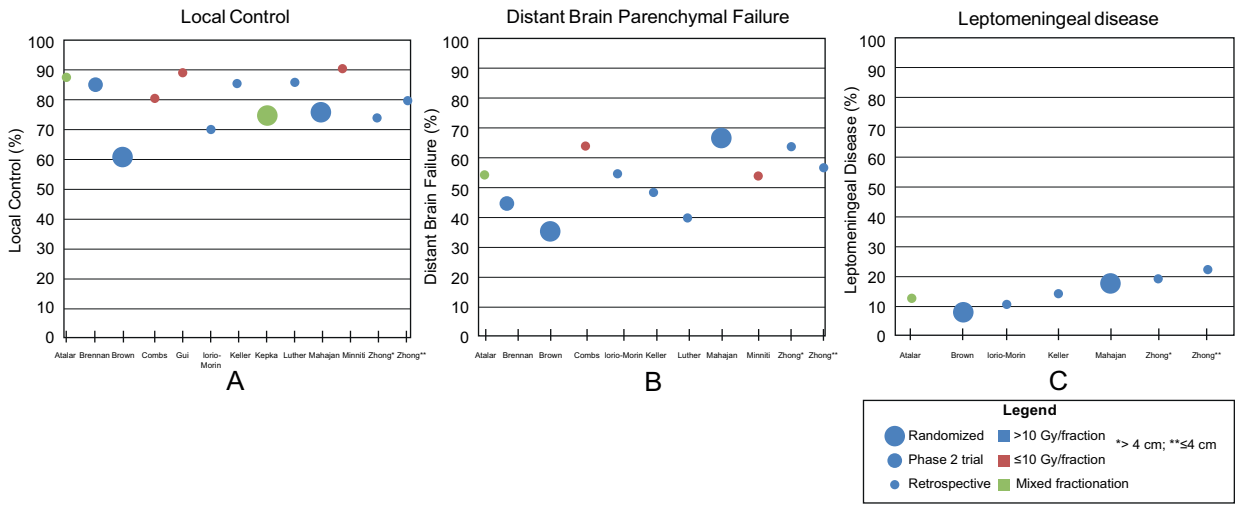

Fig. 2. Tumor control outcomes for all prospective and retrospective series summarized in this manuscript. Specifically, (A) the local control rate, (B) the rate of distant brain parenchymal failure, and (C) the rate of development of leptomeningeal disease.

SRS/SRT or observation in the management of brain metastases resection cavities. Prospective data do demonstrate superiority of SRS compared with observation in terms of LC in this setting.[7] However, although retrospective and single-institution studies suggest excellent LC ranging from 74% to 91% after postoperative SRS/SRT,[9-17] a recent randomized study demonstrated higher rates of local recurrence in patients who received SRS than in those receiving WBRT.[6] Although the reason for this outcome remains unclear, it is not surprising given that modest prescription radiation doses as low as 12 to 14 Gy in a single fraction were delivered to larger cavities. This is particularly important in the context of data that suggest that minimum doses >15 Gy in a single fraction are associated with superior LC as compared to more conservative doses.[24] Indeed, 40% of patients had surgical cavities measuring >3 cm. The biologically equivalent doses of 12 to 14 Gy in a single fraction are lower than those prescribed in the WBRT arm, thereby negating the potential dose escalation benefit of SRS in terms of LC. In addition, the application of RECIST criteria to assess response in this study may have incorrectly categorized radiosurgery-induced radiographic changes as true progression, falsely inflating the risk of recurrence in this group, whereas treatment-induced radiographic changes after WBRT are uncommon. Thus, challenges in response assessment may also explain the results that were incongruent with other series. Ultimately, future investigations comparing single-fraction SRS regimens with hypofractionated SRT regimens will be essential in determining the optimal dose fractionation schedule. It will also be important to develop response criteria specific to surgical resection cavities, as both RECIST and response assessment in neuro-oncology criteria were not intended to serve as response criteria in the dynamic postoperative setting.

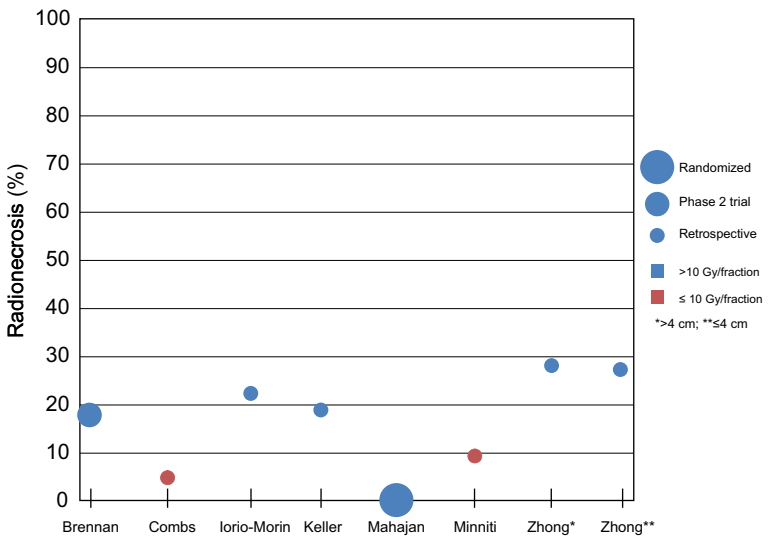

Fig. 3. Radionecrosis rate for all of the studies in which it was reported.

Since the time of data collection for this review, Kayama et al[25] published the results of a study that randomized patients with 1 to 4 brain metastases to whole-brain radiation therapy or salvage SRS to the residual metastases after surgical resection of a brain metastases. Although WBRT had longer intracranial progression-free survival compared with SRS, there was no difference in overall survival, and 16.4% of patients in the WBRT group experienced grade 2 to 4 cognitive deterioration, compared with 7.7% in the SRS group. Interestingly, LC was only 56% in both arms, which is lower than reported after WBRT in the other randomized controlled trials reviewed herein. However, it is important to note that all patients in the WBRT arm received treatment, whereas in the salvage SRS arm, physicians could choose postoperative SRS or observation alone based on their assessment of the presence of residual tumor postoperatively. Ultimately, the authors conclude that salvage SRS represents a viable alternative to WBRT after surgery for brain metastases. It is possible that the lower than anticipated rate of LC in the SRS arm of this study reflects poorer outcomes in the salvage setting than in the upfront setting, but this hypothesis remains to be evaluated in future studies.

Since the time of the eligibility criteria for our review, emerging data also suggest that fractionated SRT regimens may have improved LC over single-fraction SRS, especially for larger tumors. Although prospective data demonstrate significantly poorer LC in large tumors measuring greater than 2.5 cm preoperatively,[7] retrospective studies suggest superior LC ranging from 84% to 93% after fractionated regimens such as 27 Gy in 3 fractions or 25 to 35 Gy in 5 fractions.[16,18,20] A large multi-institutional retrospective analysis of 581 resection cavities treated with fractionated SRT to a median total dose of 30 Gy (range, 18-35 Gy) and a dose per fraction of 6 Gy (range, 5-10.7 Gy) was recently published.[26] LC was 84% at 1 year, 75% at 2 years, and 71% at 3 years.[26] This concept of fractionated SRT is the subject of an ongoing Alliance trial (NCT04114981) that is randomizing patients who have undergone complete resection of a brain metastasis measuring at least 2 cm on preoperative MRI to single-fraction SRS or fractionated stereotactic radiation therapy in either 3 or 5 fractions. The primary endpoint is time to local recurrence.

Challenges with target delineation may also contribute to the suboptimal LC of only 60.5% at 1 year in the SRS arm of the Brown et al study[6] compared with the other studies included in this manuscript. The protocol recommended a 2-mm radial expansion from the resection cavity, but at the time of study accrual, the consensus contouring guidelines summarized had not yet been published to guide CTV delineation. Furthermore, detailed communication with the neurosurgeon is essential in identifying high-risk regions after surgery for brain metastases, but neurosurgical involvement was not mandated by the clinical trial. At present, in spite of the existence of contouring guidelines, the optimal target delineation to maximize LC while minimizing toxicity remains uncertain, and additional patterns of failure analyses and, ideally, prospective data will be essential in improving patient outcomes. For example, although the consensus contouring guidelines suggest that the entire surgical corridor leading to the resection cavity be included in the target volume, a patterns of failure analysis published in the interim period failed to show differences in the rate of LC irrespective of whether the surgical corridor was targeted, although rates of LMD were lower when the surgical corridor was included.[27] In addition, a recent retrospective study suggested that T2-weighted MRI might allow better visualization of the resection cavity while reducing the volume of the target.[28]

A concern with postoperative SRS and SRT is the risk of microscopic leptomeningeal contamination with surgical manipulation, which historically was addressed using WBRT. The rate of development of LMD has ranged from 7.2% to 22.8% in the retrospective series.[9,13,14,17] A more recent large retrospective review from Stanford similarly revealed an overall incidence of LMD of 15.8%.[23] Nonetheless, the Brown et al[6] randomized study showed low rates of LMD in both arms (7.2% after SRS and 5.4% after WBRT). It is unclear whether this represents differences in surgical technique, definition of LMD, or long-term follow-up imaging between the retrospective and prospective series. A recent study showed that 72% of the deaths in patients with pachymeningeal recurrences were due to progressive pachymeningeal disease, but that 49.1% of patients survived more than a year when salvaged with radiation therapy.[29] Furthermore, evidence suggests that LMD after postoperative SRS tends to be asymptomatic and nodular rather than the classic "sugarcoating" that has historically been defined as LMD, which is associated with a dismal prognosis.[30] Indeed, salvage with focal radiation therapy appears to yield comparable overall survival to salvage WBRT, albeit with a higher rate of additional nodular leptomeningeal recurrence.[30] Retrospective data suggest that the risk of LMD may be significantly higher after SRS/SRT to resection cavities than after SRS/SRT to intact metastases.[31] The mechanism may be related to intraoperative tumor contamination and anatomic disturbance of the meninges.[31] Hemorrhagic and cystic lesions,[32] the number of brain metastases,[32,33] and breast cancer histology[32-34] may be at increased risk of LMD. It is possible that en bloc resection of brain metastases may help to mitigate this risk,[35] although additional data to explore this hypothesis and its implications on the eligibility for postoperative SRS/SRT are needed. In an attempt to further reduce this risk, an ongoing clinical trial is randomizing patients to preoperative versus postoperative SRS (NCT03741673). The primary endpoint is the 1-year LMD-free rate. Given that target delineation is more straightforward for intact metastases, LC will be an important secondary endpoint as well.

In spite of the concern for LMD risk, the increasing utilization of SRS/SRT to brain metastases resection cavities is driven by a growing body of literature raising concerns of cognitive toxicity after WBRT,[36-40] which has a direct relationship with poorer overall quality of life.[41] Indeed, the

referenced randomized study comparing postoperative SRS to WBRT showed that the 6-month rate of cognitive deterioration was 52% after SRS and 85% after WBRT. This concern cannot be minimized in the setting of increasing long-term cancer survivorship resulting from continued innovations, including advancements in systemic therapy options. Since the time of data collection, randomized data have been published showing superior preservation of cognitive function when the radiation dose to the hippocampus is limited during WBRT for brain metastases in both patients who are taking memantine[42] and patients who are not.[43] Future studies comparing outcomes after hippocampal-avoidance WBRT and resection-cavity SRS will be important.

Limitations

Only 13 of 212 candidate citations met the inclusion criteria and were deemed eligible for inclusion in this systematic review. In addition, only 3 of the included studies were prospective in nature. Thus, the majority of the data included in this study bear the weaknesses inherent to retrospective data, including patients lost to follow-up, reporting bias, and selection bias. Furthermore, these studies did not explore the impact of concurrent targeted therapy or immunotherapy on tumor and toxicity outcomes, although they are increasingly being delivered together in standard practice. Thus, additional data are needed to better understand this relationship.

Importantly, our use of the linear quadratic model to compare fractionation schemes is imperfect. First, the alpha-beta ratio of the primary tumor types that develop brain metastases represent an extremely wide range, some of which can be a lower alpha-beta ratio than normal brain.[44] We have enabled a comparison using a range of 3 alpha-beta ratios, as proposed by van Leeuwen et al.[5] Second, it is important to remember that linear quadratic and isoeffective models do not take into account the repair of sublethal damage during prolonged treatments, such as those using Gamma Knife. This has the effect of overestimating the equivalent effective dose of a single-fraction treatment by 20% or more.[45]

Equally importantly, the majority of the included studies did not use pathologic confirmation of disease status to differentiate treatment-induced radiographic changes from true tumor progression. As such, the specificity of cavities categorized as having had a local recurrence is uncertain. Nonetheless, in spite of these limitations, this review included only the highest-quality primary series to reflect the best available data published to date.

Future directions

A large number of critical questions remain unanswered. For example, is there a benefit of postoperative radiation therapy in patients with brain metastases from melanoma who undergo complete resection and receive dual-agent immunotherapy? Is postoperative radiation necessary in patients with epidermal growth factor receptor mutated non-small cell lung cancer that are naïve to tyrosine kinase inhibitors? What is the role of radiation therapy in patients with advanced extracranial disease and limited viable systemic options? Additional prospective studies and future meta-analyses using individual patient data will be essential to answer these and other nuanced questions.

Conclusions

ISRS summary recommendations suggest reasonable rates of LC with acceptable toxicity after single-fraction SRS and hypofractionated SRT to brain metastases resection cavities, with superior rates of LC compared with observation and better preservation of cognitive function than WBRT. The best available data to date suggest that doses ranging from 30 to 50 Gy $EQD2_{10}$, 50 to 70 $EQD2_5$, and 70 to 90 $EQD2_2$ are appropriate, and consensus contouring guidelines recommend treatment of the surgical cavity, plus entire surgical tract, plus an approximately 2- to 3-mm PTV expansion, with greater CTV expansions for tumor contacting the dura or sinus preoperatively. However, future investigations will be essential to better understand the relationship between WBRT and SRS/SRT in the postoperative setting, as well as to identify the most advantageous dose fractionation schedules and optimize target delineation.

Disclaimer

These guidelines should not be considered inclusive of all methods of care or exclusive of other methods of care reasonably directed to obtain similar results. The physician must make the ultimate judgment depending on the characteristics and circumstances of individual patients. Adherence to these guidelines will not ensure successful treatment in every situation. The authors of these guidelines and the International Stereotactic Radiosurgery Society assume no liability for the information, conclusions, and recommendations contained in this report.

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