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The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline.

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INVITED MANUSCRIPT

The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline

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Abstract

Question

Should patients with newly-diagnosed metastatic brain tumors undergo stereotactic radiosurgery (SRS) compared with other treatment modalities?

Target population

These recommendations apply to adults with newly diagnosed solid brain metastases amenable to SRS; lesions amenable to SRS are typically defined as measuring less than 3 cm in maximum diameter and producing minimal (less than 1 cm of midline shift) mass effect.

Recommendations

SRS plus WBRT vs. WBRT alone

Level 1 Single-dose SRS along with WBRT leads to significantly longer patient survival compared with WBRT alone for patients with single metastatic brain tumors who have a KPS $\geq$ 70.

Level 2 Single-dose SRS along with WBRT is superior in terms of local tumor control and maintaining functional status when compared to WBRT alone for patients with 1–4 metastatic brain tumors who have a KPS $\geq$ 70.

Level 3 Single-dose SRS along with WBRT may lead to significantly longer patient survival than WBRT alone for patients with 2–3 metastatic brain tumors.

Level 4 There is class III evidence demonstrating that single-dose SRS along with WBRT is superior to WBRT alone for improving patient survival for patients with single or multiple brain metastases and a KPS $<$ 70.

SRS plus WBRT vs. SRS alone

Level 2 Single-dose SRS alone may provide an equivalent survival advantage for patients with brain metastases compared with WBRT + single-dose SRS. There is conflicting class I and II evidence regarding the risk of both local and distant recurrence when SRS is used in isolation, and class I evidence demonstrates a lower risk of distant recurrence with WBRT; thus, regular careful surveillance is warranted for patients treated with SRS alone in order to provide early identification of local and distant recurrences so that salvage therapy can be initiated at the soonest possible time.

Surgical Resection plus WBRT vs. SRS ± WBRT

Level 2 Surgical resection plus WBRT, vs. SRS plus WBRT, both represent effective treatment strategies, resulting in relatively equal survival rates. SRS has not been assessed from an evidence-based standpoint for larger lesions (>3 cm) or for those causing significant mass effect (>1 cm midline shift). Level 3: Underpowered class I evidence along with the preponderance of conflicting class II evidence suggests that SRS alone may provide equivalent functional and survival outcomes compared with resection + WBRT for patients with single brain metastases, so long as ready detection of distant site failure and salvage SRS are possible.

SRS alone vs. WBRT alone

Level 3 While both single-dose SRS and WBRT are effective for treating patients with brain metastases, single-dose SRS alone appears to be superior to WBRT alone for patients with up to three metastatic brain tumors in terms of patient survival advantage.

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Rationale

A significant proportion of adults with cancer will develop brain metastases. This number is increasing as advances extend cancer patient survival leading to increasing risk-years for brain metastasis development. The precise incidence and epidemiology of metastatic brain tumors is poorly studied and understood, however, it is estimated that approximately 1.4 million Americans are diagnosed with cancer every year [1] and up to 40% of these patients—over a half million people annually—will go onto develop one or more brain metastases [2]. Solid brain tumors represent 90–95% of brain metastases with meningeal involvement accounting for the balance [3–5]. Approximately 37–50% of solid tumor patients present with single brain metastases while roughly 50–63% have multiple tumors at initial presentation [2, 6, 7]. Given that SRS can treat more than one tumor per session, and that most tumors are detected while small in size, the percentage of patients that are potential candidates for SRS is quite large.

The outcome for patients with brain metastases is generally poor, with a median survival following WBRT alone of only 3–4 months regardless of primary tumor histology (small cell lung carcinoma (SCLC) excepted) [7–18]. Indeed, after WBRT, 50% of patients still succumb to their brain tumor [14]. These results have driven efforts to improve results by exploring modalities to improve quality of life through better local control, as well as overall survival.

For patients with single accessible brain metastases, surgical resection followed by post-operative WBRT has been compared to WBRT alone in three randomized controlled trials (RCT) [13, 14, 17].The evidence for this combined treatment approach is reviewed in the WBRT guideline paper of this series by Gaspar et al. [19].

Outcomes for patients with single solid metastatic brain tumors amenable to either surgical resection or SRS have been shown to be roughly equivalent for both local control and overall patient survival [14, 15, 17, 20–26]. Open surgery has the potential for better overall outcomes for lesions >3 cm in diameter in locations amenable to resection with acceptable risk, and better and/or faster outcomes for smaller lesions causing symptomatic edema or mass effect. On the other hand, SRS may result in superior local control rates for radioresistant lesions (e.g., renal cell, melanoma, etc.), and may allow WBRT to be deferred for subsequent salvage treatment without adverse sequelae. The evidence for these conclusions is reviewed in the surgical resection guideline paper in this series by

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Kalkanis et al. [27]. SRS has the ability to treat lesions that may not be safely resectable.

Patients are generally considered candidates for SRS if the tumor(s) in question is less than 10 cc in volume (<3 cm average diameter) [20–22, 24–26]. The number of tumors that can be effectively treated with SRS in a given patient is an area still under study. SRS itself has undergone recent scrutiny to better define its boundaries. In 2006, the American Society for Therapeutic Radiology and Oncology (ASTRO), the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) jointly agreed to define SRS in a way that includes both traditional single dose SRS, as well as multi-dose SRS up to five doses (2–5 doses) [28, 29].

The surgical resection guideline paper in this series addresses the relative roles of surgical resection plus WBRT vs. SRS + WBRT for patients with single solid brain metastases. This paper will briefly summarize those findings but then expand the focus to explore patients with multiple metastases. This paper will also explore the relative need for WBRT when SRS is utilized as a sole treatment modality, the relative role of WBRT if SRS is used to augment surgical resection, as well as the relative role of multi-dose SRS vs. single dose SRS.

The overall objectives of this paper are:

To systematically review the evidence available for the following treatment comparisons for patients with newly diagnosed brain metastases.

WBRT vs. WBRT + SRS
SRS vs. WBRT +SRS
WBRT vs. SRS
SRS + WBRT vs. Resection + WBRT
SRS vs. Resection + WBRT
Other Comparisons
Multi-dose SRS vs. WBRT
Multi-dose SRS vs. Resection + WBRT or local radiotherapy (RT)
Resection + WBRT vs. Resection + SRS
Single dose SRS ± WBRT vs. Multi-dose SRS + WBRT

Methods

Search strategy

The following electronic databases were searched from 1990 to September 2008: MEDLINE®, Embase®, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Registry, Cochrane Database of Abstracts of Reviews of Effects. A broad search strategy using a combination of subheadings and text words was employed. The search strategy is documented in the methodology paper for this guideline series by Robinson et al. [30]. Reference lists of included studies were also reviewed.

Eligibility criteria

- Published in English.
- Patients with newly diagnosed brain metastases.
- Fully-published (i.e., not in abstract form) peer-reviewed primary comparative studies. (These included the following comparative study designs for primary data collection: RCTs, non-randomized trials, cohort studies, and case–control studies.
- Study comparisons include one or more of the following (local RT = fractionated radiotherapy localized to the tumor):
  - WBRT vs. WBRT + SRS
  - SRS vs. WBRT + SRS
  - SRS vs. WBRT
  - SRS ± WBRT or local RT vs. Resection ± WBRT or local RT
  - SRS ± Resection vs. WBRT ± Resection
  - Single dose SRS ± WBRT vs. Multi-dose SRS ± WBRT
- Number of study participants with newly diagnosed brain metastases ≥5 per study arm for at least two of the study arms.
- Baseline information on study participants is provided by treatment group in studies evaluating interventions exclusively in patients with newly diagnosed brain metastases. For studies with mixed populations (i.e., includes participants with conditions other than newly diagnosed brain metastases), baseline information is provided for the intervention sub-groups of participants with newly diagnosed brain metastases.

Study selection and quality assessment

Two independent reviewers evaluated citations using a priori criteria for relevance and documented decisions in standardized forms. Cases of disagreement were resolved by a third reviewer. The same methodology was used for full text screening of potentially relevant papers. Studies which met the eligibility criteria were data extracted by one reviewer and the extracted information was checked by a second reviewer. The PEDro scale was used to rate the quality of randomized trials [31, 32]. The quality of comparative studies using non-randomized designs was evaluated using eight items selected and modified from existing scales.

Evidence classification and recommendation levels

Both the quality of the evidence and the strength of the recommendations were graded according to the AANS/CNS criteria. These criteria are provided in the methodology paper to this guideline series.

Guideline development process

The AANS/CNS convened a multi-disciplinary panel of clinical experts to develop a series of practice guidelines on the management of brain metastases based on a systematic review of the literature conducted in collaboration with methodologists at the McMaster University Evidence-based Practice Center.

Scientific foundation

Overall 16,966 publications were screened. Fifty-six publications passed through the title and abstract screening to the full text screening level. Ultimately, 32 publications (31 primary studies and one companion paper) met the eligibility criteria. Figure 1 outlines the flow of the studies through the review process.

Whole brain radiotherapy alone versus whole brain radiotherapy plus stereotactic radiosurgery

Two prospective RCTs (class I evidence) [25, 33] and one retrospective cohort study with historical controls (class III evidence) [34] evaluated WBRT alone vs. WBRT + SRS for the initial management of patients with solid metastatic brain tumors. One prospective cohort study (class II evidence) evaluated WBRT alone vs. WBRT + SRS for the initial management of patients with solid metastatic brain tumors in two arms of a three-arm study that also evaluated SRS alone [35] (Table 1). One retrospective cohort study (class II evidence) evaluated WBRT alone vs. WBRT + SRS as two of the arms in a four arm study that also included SRS alone and surgery alone (Table 1) [36]. In all five of these unique studies, only single-dose SRS was evaluated, and the results cannot be assumed to apply to 2–5 dose SRS [28, 29].

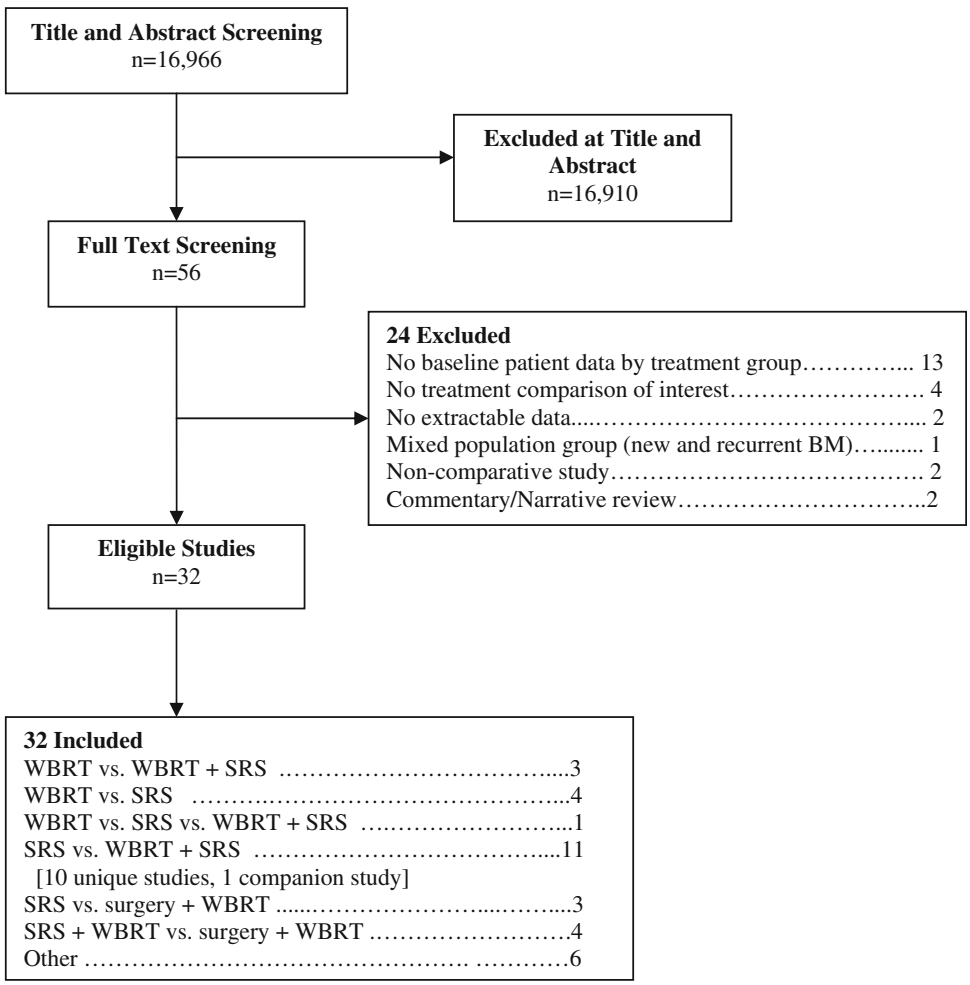

Fig. 1 Flow of studies to final number of eligible studies

Table 1 Evidence table—summary of primary studies

First author (year)	Study design Evidence class	Interventions	Population	Median survival	# Pts with recurrence/ Progression[c]	Median time to recurrence/progression
WBRT vs. WBRT + SRS						
Andrews (2004) [33]	RCT Evidence class I	G1: WBRT ($n = 167$) G2: WBRT + SRS ($n = 164$)	1–3 BM	Median survival overall: G1: 6.5 months G2: 5.7 months (Survival curves: log-rank; $p =$ NS Median survival for single BM pts: G1: 4.9 months G2: 6.5 months (Survival curves: log-rank; $p = 0.0393$)	Central review assessed 1 yr local control: G1: 71% G2: 82% ($p = 0.01$)	At original site: Median: NR (LR curves: log-rank; $p = 0.0132$) Overall in brain:Median: NR (BR curves: log-rank; $p =$ NS)
Kondziolka (1999) [25]	RCT Evidence class I	G1: WBRT ($n = 14$) G2: WBRT + SRS ($n = 13$)	2–4 BM	G1: 7.5 months G2: 11 months (Survival curves: log-rank; $p =$ NS)	1 yr local failure rate: G1: 100% G2: 8%	At original site: G1: 6 months G2: 36 months (LR curves: log-rank; $p = 0.0016$ Overall in brain: G1: 5 months G2: 34 months (Test unclear; $p = 0.002$)
Sanghavi (2001) [34]	Retrospective cohort study with historical controls Evidence class III	G1: WBRT ($n = 1200$ G2: WBRT + SRS ($n = 502$)	BM	G1: RPA class I 7.1 months G2: RPA class I 16.1 months (Greenwood's estimates; $p < 0.05$) G1: RPA class II 4.2 months G2: RPA class II 10.3 months (Greenwood's estimates; $p < 0.05$) G1: RPA class III 2.3 months G2: RPA class III 8.7 months (Greenwood's estimates; $p < 0.05$)	NR	NR
WBRT vs. SRS						
Datta (2004) [51]	Retrospective cohort study with historical controls Evidence class III	G1: WBRT ($n = 67$) G2: SRS ± WBRT ($n = 53$) [12/53 (23%) had WBRT prior to SRS]	BM	G1: 6 months G2: 6 months (Survival curves: log-rank; $p =$ NS)	NR	NR

Table 1 continued

First author (year)	Study design Evidence class	Interventions	Population	Median survival	# Pts with recurrence/ Progression[c]	Median time to recurrence/progression
Kocher (2004) [52]	Retrospective cohort study with historical controls Evidence class III	G1: SRS ($n = 117$) G2: WBRT ($n = 138$)	1–3BM	G1: RPA class I 25.4 months G2: RPA class I 4.7 months (Test not reported; $p < 0.0001$) G1: RPA class II 5.9 months G2: RPA class II 4.1 months (Test not reported; $p < 0.04$) G1: RPA class III 4.2 months G2: RPA class III 2.5 months (Test not reported; $p =$ NS)	NR by treatment groups	NR
Lee (2008) [49]	Retrospective cohort study Evidence class II	G1: WBRT ($n = 8$) G2: SRS ($n = 7$)	BM from epithelial ovarian cancer	G1: 6 months G2: 29 months (Survival curves; log-rank: $p = 0.0061$)	NR	NR
Rades (2007) [50]	Retrospective cohort study Evidence class II	G1: WBRT ($n = 91$) G2: SRS ($n = 95$)	BM	G1: 7 months G2: 13 months (Survival curves: log-rank; $p = 0.045$)	1 year local brain control rate: G1: 26% G2: 64% 1 year distant brain control rate: G1: 66% G2: 61% 1 yr overall brain control rate: G1: 23% G2: 49%	At original site: Median: Not reported by treatment group (LR curves: log-rank; $p < 0.001$) At distant brain sites: Median: Not reported by treatment group (DR curves: log-rank; $p =$ NS) Anywhere in brain: Median: Not reported by treatment group (BR curves: log-rank; $p = 0.005$)

Table 1 continued

First author (year)	Study design Evidence class	Interventions	Population	Median survival	# Pts with recurrence/ Progression[c]	Median time to recurrence/progression
WBRT vs. SRS vs. WBRT + SRS						
Li (2000) [35]	Prospective cohort study Evidence class II	G1: WBRT ($n = 19$) G2: SRS ($n = 23$) G3: SRS + WBRT ($n = 18$)	Lung cancer BM	G1: 5.7 months G2: 9.3 months G3: 10.6 months Survival curves 3 groups: log-rank; $p < 0.0001$ Survival curves G2 vs. G3: log-rank; $p =$ NS	# of pts with the following tumor response: G1: CR or PR 14/29 (48%) no change 11/29 (38%) progression 4/29 (14%) G2: CR or PR 20/23 (87%) no change 3/23 (13%) progression 0/23 G3: CR or PR 16/18 (89%) no change 2/18 (11%) progression 0/18 (3 groups: $p = 0.004$) (G2 vs. G3: $p =$ NS)	At original site: G1: 4.0 months G2: 6.9 months G3: 8.6 months (LR curves of 3 groups: log-rank; $p = 0.0000$) (LR curves G2 vs. G3: log-rank; $p =$ NS) At distant sites in brain: G1: 4.1 months G2: 6.7 months G3: 8.6 months (DR curves of 3 groups: log-rank; $p = 0.0000$) (DR curves G2 vs. G3: log-rank; p = 0.0392)
SRS vs. WBRT + SRS						
Aoyama (2006, 2007) [38, 39]	RCT Evidence class I	G1: SRS ($n = 67$) G2: WBRT + SRS ($n = 65$)	1–4BM	G1: 8.0 months G2: 7.5 months (Survival curves: log-rank; $p =$ NS)	1 year local control rate (by lesion): G1: 73% G2: 89% 1 year DR rate: G1: 64% G2: 42% 1 yr BR rate: G1: 76% G2: 47%	At distant brain site: Median: NR(DR curves: log-rank; $p = 0.003$) Overall in brain: Median: NR (BR curves: log-rank; $p < 0.001$)

Table 1 continued

First author (year)	Study design Evidence class	Interventions	Population	Median survival	# Pts with recurrence/ Progression[c]	Median time to recurrence/progression
Chidel (2000) [40]	Retrospective cohort study Evidence class II	G1: SRS ($n = 78$) G2: WBRT + SRS ($n = 57$)	BM	G1: 10.5 months G2: 6.4 months (Survival curves: log-rank; p = NS)	2 year local control rate: G1: 52% G2: 80% 2 year freedom from DR rate: G1: 48% G2: 74% 2 year freedom from BR rate: G1: 34% G2: 60%	At original site: Median: NR (LR curves: log-rank; $p = 0.034$) At distant brain site: Median: NR (DR curves: log-rank; p = NS) Overall in brain: G1: 9.2 months G2: 35.1 months (BR curves: log-rank; $p = 0.027$)
Combs (2004) [41]	Retrospective cohort study Evidence class II	G1: SRS ($n = 10$) G2: WBRT + SRS ($n = 13$) G3: SRS for recurrence ($n = 39$)	Beast cancer BM	G1: 9 months G2: 6 months G3:19 months (G1 vs. G2 survival curves log-rank: $p = 0.036$)	NR	At original site: G1: 6.5 months G2: 4.0 months G3: 9 months (G1 vs. G2 LR curves: log-rank; p = NS) At distant brain site: G1: 6.5 months G2: 4.0 months G3: 7 months (G1 vs. G2 DR curves: log-rank; p = NS)
Hoffman (2001) [42]	Retrospective cohort study Evidence class II	G1: SRS ($n = 41$) G2: WBRT + SRS ($n = 19$) G3: SRS for recurrent BM ($n = 53$)	Lung cancer BM	G1: 13.9 months G2: 14.5 months G3: 10.0 months (G1 vs. G2 cox univariate; p = NS)	1 year freedom from LR: G1: 62% G2: 88% G3: 36% 1 year freedom from DR: G1: 33% G2: 78% G3: 55% 1 year freedom from BR: G1: 13% G2: 67% G3: 27%	At original site: G1: 22.2 months G2: Not reached G3: 9.2 months (G1 vs. G2 LR curves: log-rank; p = NS) At distant brain site: G1: 8.0 months G2: Not reached G3: 16.5 months (G1 vs. G2 DR curves: log-rank; $p = 0.015$) Overall in brain: G1: 6.9 months G2: 15.0 months G3: 5.8 months (G1 vs. G2 BR curves: log-rank; 0.002)

Table 1 continued

First author (year)	Study design Evidence class	Interventions	Population	Median survival	# Pts with recurrence/ Progression[c]	Median time to recurrence/progression
Jawahar (2002) [43]	Retrospective cohort study Evidence class II	G1: SRS ($n = 43$) G2: SRS + WBRT ($n = 18$)	BM	Median: NR by treatment group (Survival curves: log-rank; p = NS)	Local tumor control: Reported no significant difference between groups [data: NR] Distant tumor recurrence: Reported no significant difference between groups [data: NR]	NR
Noel (2003) [44]	Retrospective cohort study Evidence class II	G1: SRS ($n = 34$) G2: WBRT + SRS ($n = 22$) G3: SRS for recurrence BM ($n = 36$)	BM	G1: 7 months G2: 14 months G3: 8 months (G1 vs. G2 survival curves: log-rank; p = NS)	1 year local control rate: G1: 78% G2: 94% G3: 86%	Overall in brain: G1: 13 months G2: 24 months (G1 vs. G2 BR curves: NR) G3: Not reached
Pirzkall (1998) [45]	Retrospective cohort study Evidence class II	G1: SRS ($n = 158$) G2: WBRT + SRS ($n = 78$)	1–3 BM	Median: NR by treatment group 1 year survival rates: G1: 19% G2: 30% (Survival curves: log-rank; p = NS)	1 year local control rate: G1: 89% G2: 92%	At original site: Median time: NR (LR curves: log-rank; p = NS) At distant brain site: G1: 4.3 months G2: 5.4 months (p = NR)
Sneed (1999) [46]	Retrospective cohort study Evidence class II	G1: SRS ($n = 62$) G2: WBRT + SRS ($n = 43$)	BM	G1: 11.3 months G2: 11.1 months (Survival curves: log-rank; p = NS)	At original site: G1: 13/62 (21%) G2: 7/43 (16%) At distant brain sites G1: 31/62 (50%) G2: 12/43 (28%) Overall in brain: G1: 36/62 (58%) G2: 16/43 (37%)	At original site: G1: 21.0 months G2: Not reached (LR curves: log-rank; p = NS) At distant brain sites: G1: 8.5 months G2: 16.8 months (DR curves: log-rank; $p = 0.03$) Overall in brain: G1: 8.3 months G2: 15.9 months (BR curves: log-rank; $p = 0.008$)
Sneed (2002) [47]	Retrospective cohort study Evidence class II	G1: SRS ($n = 268$) G2: WBRT + SRS ($n = 301$)	BM	G1: 8.2 months G2: 8.6 months (Univariate Cox; p = NS)	NR	NR

Table 1 continued

First author (year)	Study design Evidence class	Interventions	Population	Median survival	# Pts with recurrence/ Progression[c]	Median time to recurrence/progression
Varlotto (2005) [48]	Retrospective cohort study Evidence class II	G1: SRS ($n = 40$) G2: WBRT + SRS ($n = 70$)	Pts surviving >1 year after SRS for BM	Median: NR by group (Survival curves: log-rank; p = NS)	1 year local control (by lesion): G1: 84% G2: 93% 1 year distant recurrence rates: G1: 26% G2: 21%	At original site: Median: NR (LR curves: log-rank; $p = 0.03$) At distant brain sites: Median: NR (DR curves: log-rank; p = NS)
SRS vs. Surgery +WBRT						
Muacevic (2008) [57]	RCT Evidence class I	G1: Surgery + WBRT ($n = 33$) G2: SRS ($n = 31$)	Single BM	G1: 9.5 months G2: 10.3 months (Survival curves: log-rank; p = NS)	1 year freedom from local recurrence/ progression rates: G1: 82% G2: 97% 1 year distant recurrence/ progression rates: G1: 3% G2: 26%	Median time to local recurrence in brain: Not reported (LR curves: log-rank; p = NS) Median time to distant recurrence in brain: Not reported (DR curves: log-rank; $p < 0.05$)
Muacevic (1999) [58]	Retrospective cohort study Evidence class II	G1: SRS ($n = 56$) G2: Surgery + WBRT ($n = 52$)	Single BM	G1: 35 weeks G2: 68 weeks (Survival curves: log-rank; p = NS)	1 year freedom from LR rate: G1: 83% G2: 75% 1 year freedom from DR rate: G1: 68% G2: 90% ($p = 0.0025$)	At original site: G1: Median not reached G2: Median not reached (LR curves: log-rank; p = NS) At distant site: NR
Rades (2007) [59]	Retrospective cohort study Evidence class II	G1: SRS ($n = 94$) G2: Surgery + WBRT ($n = 112$)	Single BM	Median survival: NR 1 year survival rate: G1: 54% G2: 38% (Survival curves: log-rank; p = NS)	1 year freedom from LR rate: G1: 64% G2: 56% 1 year freedom from BR rate: G1: 49% G2: 44%	At original site: Median: NR (LR curves: log-rank; p = NS) Overall in brain: Median: NR (BR curves: log-rank; p = NS)

Table 1 continued

First author (year)	Study design Evidence class	Interventions	Population	Median survival	# Pts with recurrence/ Progression[c]	Median time to recurrence/progression
SRS + WBRT vs. Surgery +WBRT						
Bindal (1996) [53]	Retrospective cohort study Evidence class II	G1: Surgery ± WBRT[a](n = 62) [matched to G2] G2: SRS ± WBRT[a] ($n = 31$)	Single BM	G1: 16.4 months G2: 7.5 months (Survival curves:log-rank; $p = 0.0018$)	1 year freedom from LR rate: G2 poorer than G1 [Data: NR] 1 year freedom from DR rate: G1: 75% G2: 69%	At original site: G1: Median not reached G2: 6 months (LR curves: log-rank; $p = 0.0001$) At distant brain sites: G1: Median not reached G2: Median not reached (DR curves: log-rank; $p =$ NS)
Garell (1999) [54]	Retrospective cohort study Evidence class II	G1: Surgery + WBRT ($n = 37$) G2: SRS + WBRT ($n = 8$)	Single BM	G1: 8 months G2: 12.5 months (Survival curves:log-rank; $p =$ NS)	NR	NR
O'Neill (2003) [55]	Retrospective cohort study Evidence class II	G1: Surgery[a] ± WBRT ($n = 74$) G2: SRS[a] ± WBRT ($n = 23$)	Single BM	Median survival: NR 1 year survival rate: G1: 62% G2: 56% (Survival curves: log-rank; $p =$ NS)	At original site: G1: 11/64 (17%) G2: 0/21 ($p =$ NR) Overall in brain: G1: 19/64 (30%) G2: 6/21(29%) ($p =$ NR)	NR
Schoggl (2000) [56]	Retrospective cohort study Evidence class II	G1: Surgery + WBRT ($n = 66$) G2: SRS + WBRT ($n = 67$)	Single BM	G1: 9 months G2: 12 months (Survival curves: test unclear[b]; $p =$ NS)	At original site: G1: 11/66 (17%) G2: 3/67 (5%) ($p =$ NR) At distant brain sites: G1: 10/66 (15%) G2: 7/67 (10%) ($p =$ NR)	At original site: G1: 3.9 months G2: 4.9 months (LR curves: test unclear[b] $p < 0.05$) At distant brain sites: G1: 3.7 months G2: 4.4 months (DR curves: test unclear[b] $p =$ NS)
Other						
De Salles (1993) [62]	Retrospective cohort study Evidence class II	G1: SRS ± WBRT ($n = 19$) G2: SFR ± WBRT ($n = 7$)	BM	Median: NR Average survival: G1: 8 months G2: 7 months (p-value: NR)	At distant sites in brain: G1: 4/19 (21%) G2: NR	NR

Table 1 continued

First author (year)	Study design Evidence class	Interventions	Population	Median survival	# Pts with recurrence/ Progression[c]	Median time to recurrence/progression
Ikushima (2000) [64]	Retrospective cohort study Evidence class II	G1 : SFR ($n = 10$) G2: Surgery + RT ($n = 11$) G3: RT ($n = 14$) [RT = WBRT or local]	RCC BM	G1: 25.6 months G2: 18.7 months G3: 4.3 months (Univariate analysis[d]:G1 vs. G2 + G3: $p = 0.05$)	1 year local control rate: G1: 90% G2: 88% G3: NR	At original site: Median: NR (LR curves: log-rank; $p = NS$)
Lindvall (2005) [63]	Retrospective cohort study with historical controls Evidence class III	G1: SFR ($n = 47$) G2: WBRT + SRS or SFR ($n = 14$)	BM	G1: 5.0 months G2: 5.0 months(Survival curves: log-rank; $p = NS$)	Local response (by lesion) in the pts with available data: G1: stable 37/44 (84%) progression 7/44 (16%) G2: stable 11/11 (100%) progression 0/11 ($p = NS$) # of pts with recurrence at distant sites: G1: 8/32 (25%) G2: 0/11 ($p = 0.0005$)	NR
Serizawa (2000) [61]	Retrospective cohort study Evidence class II	G1: WBRT ± surgical resection ($n = 34$) G2: SRS ± surgical resection ($n = 62$)	NSCLC BM	G1: 199 days G2: 377 days (Survival curves: log-rank: $p = 0.0158$)	1 year tumor control rates: G1: NR G2: 94.8%	At distant sites in brain: G1: 539 days G2: 422 days (DR curves: log-rank; $p = NS$)
Shinoura (2002) [60]	Retrospective cohort study Evidence class II	G1: SRS ($n = 28$) G2: Surgery + RT ($n = 35$) [RT = WBRT or local]	BM	G1: 8.2 months G2: 34.4 months (Survival curves: log-rank; $p < 0.0001$)	# lesions that recurred at original site: G1: 16/52 (31%) G2:14/46 (30%) ($p = NR$)	Mean time to recurrence at original site: G1: 7.2 months G2: 25 months (LR curves: log-rank; $p = 0.0199$)

Table 1 continued

First author (year)	Study design Evidence class	Interventions	Population	Median survival	# Pts with recurrence/ Progression[c]	Median time to recurrence/progression
Wang (2002) [36]	Retrospective cohort study Evidence class II	G1: Surgery G2: WBRT G3: SRS G4: SRS + WBRT	BM	G1: 43.0 weeks G2: 37.0 weeks G3: 67.0 weeks G4: 91.0 weeks (Survival curves: log-rank; $p < 0.00001$)	Local tumor control at 1 month: G1: 89% G2: 88% G3: 93% G4: 96% (p = NR)	NR

BM Brain metastases, *BR* Brain recurrence (local + distant), *CR* Complete response, *DR* Distant recurrence in brain, *G1* Group 1, *G2* Group 2, *G3* Group 3, *G4* Group 4, *LR* Local recurrence at original site in brain, *NSCLC* Non-small cell lung cancer, *NR* Not reported, *NS* Not significant, *PR* Partial response, *Pts* Patients, *RCC* Renal cell carcinoma, *RCT* Randomized control trial, *RPA* Recursive partitioning analysis, *RT* Radiotherapy, *SFR* Stereotactic fractionated radiotherapy, *SRS* Stereotactic radiosurgery, *WBRT* Whole-brain radiation therapy

[a] WBRT use similar at baseline in both groups

[b] Either log-rank or Wilcoxon test

[c] Number of pts with recurrence/progression of brain metastases, unless otherwise specified

[d] Univariate analysis using Cox proportional hazard model

The first RCT is a Radiation Therapy Oncology Group (RTOG) multi-center trial led by Andrews et al., published in 2004 [33]. The trial randomized adults with a Karnofsky performance status (KPS) $\geq$ 70 with 1–3 solid brain metastases with a maximum diameter of 4 cm for the largest and $\leq$3 cm for the remainder. Patients were stratified by number of metastases and extent of extra-cranial disease. WBRT and SRS doses were standard. Overall follow-up was a median of 12 months. Patient groups were well matched for sex, age (19–90 years), histology, KPS, and mini-mental status exam (MMSE) score. There were 164 patients in the WBRT + SRS arm (of which 31/164 (19%) did not receive their planned SRS) and 167 patients in the WBRT alone arm (of which 28/167 (17%) received salvage SRS). The primary endpoint was median survival. Secondary endpoints included tumor control at 1 year, KPS and MMSE at 6 months and cause of death (neurologic vs. non-neurologic). This trial can be criticized for a large bilateral crossover rate in an intent-to-treat model, no follow-up neuroimaging review on 43% of patients, and inclusion of tumors >3 cm diameter which are known to be less favorable for SRS but were included in the original RTOG 90-05 trial and were included for that reason (refer to the surgical resection guideline paper by Kalkanis et al. [27]. Nevertheless, this trial demonstrated significantly better survival for patients with single metastatic tumors ($p = 0.01$), superior local control for patients with 1–3 metastatic brain tumors ($p = 0.01$), and improved KPS for patients with 1–3 metastatic brain tumors in the WBRT + SRS arm. The last two conclusions were secondary endpoints assessed with post hoc analysis and thus, are not as strong as the single tumor survival conclusion. There was no significant difference between groups in median survival for patients with 2–3 brain tumors, MMSE at 6 months, incidence of neurologic cause of death, or adverse therapeutic events [33]. However, because of the large follow-up loss in this study, no conclusion can be assured.

The second RCT is a single institution study from the University of Pittsburgh led by Kondziolka et al., published in 1999 [25]. The trial randomized adults with a KPS $\geq$ 70 with 2–4 solid metastatic brain tumors, each $\leq$2.5 cm in mean diameter. WBRT and SRS doses were standard. Overall follow-up was not reported. Patient groups were well matched for sex, age (33–77 years), histology, number of brain tumors, KPS score, and extent of systemic disease. There were 14 patients in the WBRT arm and 13 in the WBRT + SRS arm. All patients completed the treatment in their intent-to-treat arm. Since the primary endpoint was imaging-defined local control, no patient received salvage SRS until they were censored for analysis. Secondary endpoints included median survival, and time to recurrence/progression at the original tumor

sites. The study was stopped at the 60% accrual point due to an overwhelmingly positive tumor control difference at interim analysis. This trial demonstrated significantly better local control rates measured in terms of local failure at 1 year (8 vs. 100%) and median time to recurrence/progression at original site (36 vs. 6 months) for patients in the WBRT + SRS arm. Since the study was stopped at 60% accrual, its statistical power to assess differences in median survival was limited. Despite a large trend of 11 vs. 7.5 months favoring WBRT + SRS, this result did not achieve statistical significance due to the relatively low number of patients. Functional performance outcome, cause of death, and incidence of adverse events were not reported [25].

In the three arm prospective cohort study by Li et al. [35] recruitment was restricted to patients with both small cell- and non-small-cell lung cancer (NSCLC) and single brain metastases $\leq$4.5 cm diameter in adults with a KPS $\geq$ 60, two of the three arms were WBRT ($n = 19$) vs. WBRT + SRS ($n = 18$). Groups were similar in terms of sex, age, histology, extent of extracranial disease, and KPS score. WBRT doses and SRS doses were standard. The median survival advantage for WBRT + SRS was highly significant ($p < 0.0001$) as was the advantage for local tumor control ($p = 0.004$) and median time to progression for the treated tumor ($p < 0.00001$).

The four arm retrospective cohort study by Wang et al. [36] evaluated adult patients with 1–6 metastases of varying histologies, each <4 cm in diameter, and a KPS of 40–90; two of the four arms were WBRT alone ($n = 120$) vs. WBRT + SRS ($n = 83$). Groups were similar in terms of sex and age. Primary histology, KPS score, and extent of systemic disease were not reported by treatment group. The WBRT + SRS had significantly more patients with multiple brain tumors (50/83) than the WBRT alone arm (34/120). WBRT doses and SRS doses were standard. While 1 month local tumor control rates were similar between groups (95.6 vs. 88.3%), median survival significantly favored the WBRT + SRS group (91 vs. 37 weeks).

Sanghavi et al. [34] performed a large retrospective cohort trial ($n = 502$) of patients with varying histologies with historical controls based on recursive partitioning analysis (RPA) [37] of a database of patients from RTOG trials ($n = 1{,}200$) where patients received WBRT alone. Groups were stratified by RPA class. Groups were similar in age, and extent of extracranial disease. The WBRT group had slightly lower KPS scores, while the WBRT + SRS group had a greater percentage of radioresistant histologies (e.g., melanoma). They found statistically significant improvements in survival for patients in all three RPA classes, suggesting a survival benefit for SRS + WBRT even in patients with >1 metastatic brain tumor, the presence of systemic disease, and low KPS score.

Stereotactic radiosurgery alone versus whole brain radiotherapy plus stereotactic radiosurgery

One prospective RCT (class I evidence) with a companion paper [38, 39], and nine retrospective cohort studies (class II evidence) [40–48] evaluated SRS alone vs. WBRT + SRS for the initial management of patients with solid metastatic brain tumors. One prospective cohort study (class II evidence) evaluated SRS alone vs. WBRT + SRS for the initial management of patients with solid metastatic brain tumors in two arms of a three-arm study that also evaluated WBRT alone [35] (Table 1). One retrospective cohort study (class II evidence) evaluated SRS alone vs. WBRT + SRS as two of the arms in a four arm study that also included WBRT alone and surgery alone (Table 1) [36]. In all 12 of these unique studies, only single-dose SRS was evaluated, and the results cannot be assumed to apply to 2–5 dose SRS [28, 29].

The RCT is a multi-institutional study from Japan led by Aoyama et al., published in 2006 [38, 39]. The trial randomized adults with a KPS $\geq$ 70 with 1–4 solid brain metastases with a maximum diameter of $\leq$3 cm. Follow-up was 20.7 months for the SRS arm and 30.5 months for the WBRT + SRS arm. Isolated WBRT and SRS alone doses were standard, however, the SRS dose was reduced by 30% in the WBRT + SRS arm relative to the SRS alone arm. Patient groups were similar in terms of sex, age, histology, number of tumors, extent, and stability of extracranial disease, primary tumor status, KPS score, and MMSE score. There were 67 patients in the SRS alone arm (of which 2/67 (3%) did not receive SRS, and 11/67 (16%) received WBRT as a salvage therapy) and 65 in the WBRT + SRS arm (of which 6/65 (9%) did not receive SRS, 2/65 (3%) did not receive WBRT, and 10/65 (15%) received additional salvage SRS). The primary endpoint was median survival. Secondary endpoints included 1 year tumor control rate, 1 year recurrence rate at untreated sites, neurologic cause of death, 1 year KPS score, 1 year MMSE score, and adverse event rate. This trial can be criticized for a large bilateral crossover rate in an intent-to-treat model. Results revealed no significant difference between study groups for median survival (8.0 vs. 7.5 months), 1 year local control rate (72.5 vs. 88.7%), neurologic cause of death, 1 year KPS score, MMSE score, or acute or late neurotoxicity. However, the 1 year chance of recurrence locally (27.5 vs. 11.3%), at a distant site (63.7 vs. 41.5%), or anywhere in the brain (76.4 vs. 46.8%) was significantly greater for the SRS alone arm than the WBRT + SRS arm, as was the chance of requiring additional salvage therapy in the form of either SRS or WBRT (43.3 vs. 15.4%). In a second, secondary endpoint analysis publication from the same study looking at the 70% subset of patients with initial and follow-up MMSE examinations,

and then restricting analysis still further to the 62% of patients with pre-treatment MMSE scores of ≥27 or who improved on follow-up to MMSE scores ≥27, the addition of up-front WBRT significantly increased the time to MMSE deterioration, which was often due to distant tumor recurrence [39].

In the three arm prospective cohort study by Li et al. [35] recruitment was restricted to patients with both SCLC and NSCLC, and single brain metastases ≤4.5 cm diameter in adults with a KPS ≥ 60; two of the three arms were SRS ($n = 23$) vs. WBRT + SRS ($n = 18$). Groups were similar in terms of sex, age, histology, extent of extracranial disease, and KPS score. WBRT doses and SRS doses were standard. There was no significant difference between the two groups in terms of median survival (9.3 vs. 10.6 months) or in terms of recurrence/progression at the treated site. Distant brain recurrence was not assessed.

Of the 10 retrospective cohort studies addressing this comparison in patients with both single and multiple brain metastases of varying histologies, nine are direct comparisons of SRS alone vs. WBRT + SRS [40–48] and one is a four arm retrospective cohort study with SRS and WBRT + SRS as two of the four comparison arms [36]. Of these 10 studies, eight show no significant difference in median survival between both treatment options with ranges for median survival of 7–13.9 months and 6.4–14.9 months, respectively [40, 42–48]. One study of patients with breast cancer brain metastases showed improved median survival of 9 vs. 6 months favoring SRS alone [41], and another studying tumors of varying histology showed improved median survival of 91 vs. 67 weeks favoring WBRT + SRS [36]. Of the 10 studies, only one (which studied only patients who had survived >1 year since treatment) revealed a statistically significant increase in local recurrence rate or reduced time to local recurrence [48]. However, four revealed either increased distant brain or overall brain recurrence rates and/or reduced time to distant brain or overall brain recurrence [40, 42, 44, 45]. On the other hand, the study of patients who had survived >1 year since treatment suggested that while the median time to local recurrence/progression was significantly increased with SRS alone, the median time to distant recurrence was not significantly different between the two arms [48].

Stereotactic radiosurgery alone versus whole brain radiotherapy alone

No RCTs were identified that met the eligibility criteria for this treatment comparison. One prospective cohort study (class II evidence) evaluated SRS alone vs. WBRT alone for the initial management of patients with solid metastatic brain tumors in two arms of a three-arm study that also evaluated WBRT + SRS [35]. There were two retrospective cohort studies with concomitant control groups (class II evidence) that compared SRS alone vs. WBRT alone (Table 1) [49, 50]. There were two retrospective cohort studies with historical controls (class III evidence) that compared SRS alone vs. WBRT alone (Table 1) [51, 52]. One retrospective cohort study (class II evidence) evaluated SRS alone vs. WBRT alone as two of the arms in a four arm study that also included WBRT + SRS and surgery alone (Table 1) [36]. In all of these unique studies, only single-dose SRS was evaluated, and the results cannot be assumed to apply to 2–5 dose SRS [28, 29].

The three arm prospective cohort study by Li et al. (2000) [35] evaluated adult patients with both SCLC and NSCLC, and single brain metastases ≤4.5 cm diameter in adults with a KPS ≥ 60, two of the three arms were SRS alone ($n = 23$) vs. WBRT alone ($n = 19$). Groups were similar in terms of sex, age, histology, extent of extracranial disease, and KPS score. WBRT doses and SRS doses were standard. The SRS alone arm had significantly longer median survival (9.3 vs. 5.7 months), neuroimaging tumor response (complete or partial response 87 vs. 38%, and progression 0 vs. 14%), and median time to progression (6.9 vs. 4.0 months). Distant brain recurrence was not assessed.

In the small retrospective cohort study by Lee et al. [49] recruitment was restricted to patients with 1–12 non-germ cell epithelial ovarian cancer brain metastases; 15 patients were treated with either SRS alone ($n = 7$) or WBRT alone ($n = 8$). Groups were poorly analyzed in terms of potentially relevant intergroup differences and SRS and WBRT dosing parameter was not provided. Despite these issues, the authors reported a significantly improved median survival outcome for the SRS arm (29 vs. 6 months for WBRT alone).

In the large retrospective cohort study by Rades et al. [50] 186 patients with 1–3 brain metastases of varying histologies ≤4 cm diameter received either WBRT alone ($n = 91$) or SRS alone ($n = 95$). Groups were well matched for sex, age, RPA class, number of metastases, extent of extracranial disease, baseline functional performance, and histology. Median survival was significantly longer for the SRS alone group (13 vs. 7 months for WBRT alone). One-year local and overall brain control rates were likewise significantly better for the SRS alone arm (64 vs. 26% and 49 vs. 23%, respectively). Distant brain control rates were similar for both groups (66% WBRT alone vs. 61% SRS alone). Toxicity rates were similar for both groups.

The four arm retrospective cohort study by Wang et al. [36] evaluated adult patients with one or more brain metastases of varying histologies, each <4 cm in diameter

and a KPS > 50. Two of the four arms were SRS alone ($n = 130$) vs. WBRT alone ($n = 120$). Groups were similar in terms of sex and age. Primary histology, KPS score, and extent of systemic disease were not reported by treatment group. The SRS treatment group had more patients with multiple brain tumors (50/83) than the WBRT alone arm (34/120). WBRT doses and SRS doses were standard. While 1 month local tumor control rates were similar between groups (93.3 vs. 88.3%), median survival significantly favored the SRS group (67 vs. 37 weeks).

Kocher et al. [52] performed a retrospective cohort trial of SRS ($n = 117$) compared against 138 WBRT historic control patients treated 1–20 years previously at the same institution for brain metastases patients with multiple histologies and ≤3 tumors. Groups were similar in terms of sex and age and were stratified according to RPA classification which accounted for extent of extra-cranial disease, number of tumors, and functional status [37]. The SRS alone arm had more melanoma patients (27 vs. 6%). WBRT and SRS doses were standard. They reported significantly better results with SRS alone for RPA class I (25.4 vs. 4.7 months) and RPA class II (5.9 vs. 4.1 months). Difference in results for RPA class III (4.2 vs. 2.5 months) did not reach statistical significance.

Datta et al. [51] performed a retrospective cohort trial of SRS ± WBRT (12/53 (22.6%) received WBRT) compared against 67 WBRT historic control patients treated 1–3 years previously at the same institution for brain metastases patients with multiple histologies and <4 tumors each <30 cc in volume. Groups were similar in terms of sex and age, but differed in terms of lung and breast cancer histology (67.9 vs. 83.6%). Number of brain tumors, extent of extracranial disease, and baseline performance status were not reported. WBRT and SRS doses were standard. They reported similar median survival of only 6 months for both groups.

Stereotactic radiosurgery plus WBRT versus resection plus WBRT

No prospective studies were identified that met the eligibility criteria for this treatment comparison. There were four retrospective cohort studies (class II evidence) that evaluated SRS + WBRT vs. resection + WBRT for the initial management of patients with solid metastatic brain tumors (Table 1) [53–56]. In all four of these unique studies, only single-dose SRS was evaluated, and the results cannot be assumed to apply to 2–5 dose SRS [28, 29].

Bindal et al. [53] performed a retrospective cohort trial of 62 patients with single brain metastases <3 cm in diameter treated with resection ± WBRT matched for sex, age, histology, KPS, and extent of disease to 31 patients undergoing SRS ± WBRT. WBRT was used in 66% of patients in the first arm and 71% of patients in the second. WBRT and SRS doses were standard. In this study, resection + WBRT achieved significantly longer median survival (16.4 vs. 7.5 months) and median time to recurrence, as well as significantly lower rates of neurologic death (19 vs. 50%) and adverse event rates than SRS + WBRT. This study reported significantly lower median survival rates (only 7.5 months), as well as higher radiation necrosis rates (12.9%), than have ever been reported by other studies evaluating single brain metastases treated with SRS + WBRT. Given the poor compliance with completion of WBRT in both arms, this study warrants retrospective down-grading to a class III evidence level, a study with flawed internal validity.

In contrast, Garell et al., (1999) (1–2 tumors each <3 cm diameter, $n = 45$), O'Neill et al., (2003) (single tumors <3.5 cm, $n = 97$), and Schoggl et al., (2000) (single tumors <3 cm diameter, $n = 133$) each reported retrospective cohort studies of patients with brain metastases with very different results [54–56]. Median survival was not significantly different but favored SRS + WBRT in two (12.5 vs. 8 months and 12 vs. 9 months, respectively) [54, 56], while 1 year survival was not significantly different but slightly favored resection + WBRT (62 vs. 56%) in the third [55]. Median time to recurrence, incidence of neurologic death, and incidence of acute and long term adverse events were similar in both arms for the Mayo Clinic study [55]. Median time to local recurrence was significantly shorter (3.9 vs. 4.9 months) and the incidence of neurologic death was greater (21.8 vs. 12.5%) in the resection + WBRT arm in the University of Vienna study, while adverse event rates were similar [56]. Cause of death and adverse event rates were not reported for the University of Iowa study [54], median time to recurrence was not reported in either the University of Iowa or the Mayo Clinic Studies [54, 55], and functional performance results were not reported in any of the three [54–56].

Stereotactic radiosurgery alone versus resection plus WBRT

One prospective RCT (class I evidence) [57], and two retrospective cohort studies (class II evidence) evaluated SRS alone vs. resection + WBRT for the initial management of patients with solid metastatic brain tumors (Table 1) [58, 59]. One retrospective cohort study (class II evidence) evaluated SRS alone vs. resection + WBRT or local RT for the initial management of patients with solid metastatic brain tumors (Table 1) [60]. These four unique studies only evaluated single-dose SRS, and the results cannot be assumed to apply to 2–5 dose SRS [28, 29].

Muacevic et al., (2008) performed a multicenter prospective RCT evaluating patients with single metastatic brain tumors, ≤3 cm diameter located in an operable site, treated with either SRS alone ($n = 31$) or resection + WBRT ($n = 33$) [57]. Groups were similar in terms of sex, age, histology, extent of systemic disease, and KPS score. WBRT and SRS doses were standard. There was no significant difference in outcome between the two groups in terms of functional performance outcome, rate of neurological death, or median survival (9.5 months surgery + WBRT vs. 10.3 months SRS). However, the study was stopped early at only 25% accrual and was therefore underpowered to detect <15% differences in outcome between groups. The SRS patients did experience an increased number of distant tumor recurrences (25.8 vs. 3%), but these occurrences did not impact overall outcome when subsequent salvage SRS was taken into account. The resection + WBRT group did experience a significantly larger number of grade 1 or 2 early and late complications compared with the SRS group.

Rades et al. [59] performed a retrospective cohort study of SRS alone ($n = 94$) vs. resection + WBRT ($n = 112$), for RPA class I or II patients with metastatic brain tumors ≤4 cm in diameter. Groups were similar in terms of sex, age, histology, number of brain tumors, extent of systemic disease, and KPS score. WBRT and SRS doses were standard. Despite a trend favoring SRS alone, there was no significant difference in outcome between groups for 1 year survival (54 vs. 38%). There was no significant difference in outcomes for 1 year local recurrence rate (36 vs. 44%) or incidence of adverse events. Functional performance and neurologic cause of death outcomes were not reported.

Muacevic et al., (1999) performed a retrospective cohort study of SRS alone ($n = 56$) vs. resection + WBRT ($n = 52$), for patients with single metastatic brain tumors ≤3.5 cm in diameter and with stable systemic disease [58].Groups were similar in terms of sex, age, extent of systemic disease, and KPS score. The SRS alone group had a slightly higher proportion of patients with melanoma (28.6 vs. 13.5%). WBRT and SRS doses were standard. Despite a trend favoring resection + WBRT, there was no significant difference in outcome between groups for median survival (35 vs. 68 weeks). There was no significant difference in outcomes for 1 year local recurrence rate (17 vs. 25%), median time to recurrence, functional performance score, or incidence of adverse events.

Shinoura et al., (2002) performed a retrospective cohort study of SRS alone ($n = 52$) vs. resection + either WBRT or local RT ($n = 46$, WBRT vs. local RT ratios not reported) for patients with one or more metastatic brain tumors <3 cm in diameter [60]. Groups were similar in terms of sex, age and histology, but the SRS alone group had more patients with multiple tumors (77 vs. 37%). Extent of extracranial disease and functional status were not reported. WBRT, local RT, and SRS doses were standard. They reported significantly longer median survival rates (34.4 vs. 8.2 months) as well as longer mean time to recurrence rates (25 vs. 7.2 months) for the resection + RT arm. Cause of death and incidence of adverse events were not reported.

Other comparisons

While our study group was interested in evaluating many more treatment comparisons (including the effectiveness of surgery plus SRS vs. resection plus WBRT, the effectiveness of substituting 2–5 dose SRS or fractionated stereotactic radiotherapy (6–9 dose) for single dose SRS, and the effectiveness of substituting local fractionated radiotherapy for WBRT) in various paradigm combinations, none of these comparisons yielded more than one clinical study for analysis, and some none at all. As a result, few conclusions can be drawn at an evidence-based medicine clinical practice parameter guideline level. Those few studies where evidence exists are presented here for completeness and interest sake and will be discussed further below in the section on "Key Issues for Further Investigation".

Resection plus whole brain radiotherapy versus resection plus stereotactic radiosurgery

No prospective studies were identified that met the eligibility criteria for this treatment comparison. There was one retrospective cohort study (class II evidence) that evaluated resection + WBRT or local RT vs. SRS alone for the initial management of patients with solid metastatic brain tumors (Table 1) [61]. In this study, only single-dose SRS was evaluated, and the results cannot be assumed to apply to 2–5 dose SRS [28, 29].

Serizawa et al. [61] performed a retrospective cohort study of resection + WBRT ($n = 34$) vs. resection + SRS ($n = 62$) for NSCLC patients with multiple brain metastases ≤3 cm in diameter in patients estimated to have at least 2 months to live. Groups were similar in terms of sex, age, number of brain tumors, extent of systemic disease, and KPS score. WBRT and SRS doses were standard. The resection + SRS alone group had significantly longer median survival (377 vs. 199 days). Unfortunately this result is difficult to evaluate given that the number of patients in the resection + WBRT arm that had resection of all tumors vs. resection of only some of the 1–10 tumors per patient were not defined. The resection + SRS arm also showed significantly longer neurological survival rates. Local tumor control rates were not reported.

Single-dose stereotactic radiosurgery versus multi-dose stereotactic radiosurgery plus whole brain radiotherapy

No prospective studies were identified that met the eligibility criteria for this treatment comparison. There was one retrospective cohort study (class II evidence) that evaluated single-dose SRS alone vs. multi-dose SRS + WBRT for the initial management of patients with solid metastatic brain tumors (Table 1) [62].

De Salles et al. [62] performed a retrospective cohort study of SRS alone ($n = 19$) vs. WBRT + multi-dose SRS ($n = 7$) in patients with multiple histologies with one or more metastatic brain tumors with volumes ranging from 0.09 to 51.84 cc (average volume 21.2 cc). Groups were similar in terms of sex and age, but the SRS alone arm had more melanoma patients (16 vs. 0%) and had significantly more multiple brain tumor patients (34 tumors in 19 patients vs. seven tumors in seven patients). WBRT and single-dose SRS doses were standard. The multi-dose SRS regimen was 6 Gy per dose given in 2–3 doses over 2–3 days. There was no significant difference in average survival between both arms (8 vs. 7 months); however, this study was underpowered to detect all but a very large difference.

Multi-dose stereotactic radiosurgery versus whole brain radiotherapy plus either single- or multi-dose SRS

No prospective studies were identified that met the eligibility criteria for this treatment comparison. There was one retrospective cohort study with historical controls (class III evidence) that evaluated multi-dose SRS vs. WBRT for the initial management of patients with solid metastatic brain tumors (Table 1) [63].

Lindvall et al. [63] performed a retrospective cohort study of multi-dose SRS alone vs. WBRT + either single- or multi-dose SRS in patients with 1–3 brain metastases of varying histologies ranging in volume from 0.9 to 41 cc (median volume 5 cc). Groups were similar in terms of sex, extent of systemic disease, and KPS score. The multi-dose SRS arm had younger patients (61.7% $\geq$ 60 vs. 85.7% $\geq$ 60), fewer melanoma patients (4.3 vs. 21.4%), fewer RPA class I patients (4.3 vs. 21.4%) and more patients with multiple brain tumors (23.4 vs. 14.2%). The WBRT dose was standard. The multi-dose SRS regimen was 40 Gy in five 8 Gy doses. The single- or multi-dose boost regimen after WBRT was given in 1–3 doses of 6–12 Gy (mean total dose 17 Gy). There was no significant difference in outcomes between groups for median survival (5 vs. 5 months) or local progression (16 vs. 0%). There was a significantly larger distant recurrence rate for the multi-dose SRS alone arm (25 vs. 0%).

Fractionated stereotactic radiotherapy alone versus resection with either whole brain radiotherapy or local radiotherapy versus whole brain radiotherapy or local radiotherapy alone

No prospective studies were identified that met the eligibility criteria for this treatment comparison. There was one retrospective cohort study (class II evidence) that evaluated fractionated stereotactic radiotherapy (FSR) alone vs. resection plus WBRT or local RT vs. WBRT or local RT alone, for the initial management of patients with solid metastatic brain tumors (Table 1) [64].

Ikushima et al. [64] performed a three arm retrospective cohort study in patients with 1–3 renal cell carcinoma brain metastases each $\leq$3 cm in diameter in adult patients with an Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2, comparing FSR ($n = 10$) vs. resection + either WBRT or local RT vs. WBRT or local RT alone. Patients were similar in terms of sex, age, and extent of extracranial disease. The FSR alone arm had more patients with single brain tumors, and the WBRT or local RT alone arm had less patients with multiple brain tumors than the resection + either WBRT or local RT arm (90 vs. 70% and 50 vs. 36%, respectively). The WBRT or local RT alone arm had more ECOG performance status two patients than either the resection + either WBRT or local RT, or the FSR alone arm (50 vs. 18 vs. 0%). The WBRT and local RT doses were standard. The FSR regimen was 42 Gy in seven fractions (6 Gy per fraction) over 2.3 weeks. While 1 year tumor control rates where similar for the FSR alone and the resection + either WBRT or local RT arms (89.6 vs. 87.5%), the FSR group had a significantly longer median survival (25.6 months) than either the surgery + either WBRT or local RT (18.7 months), or the WBRT or local RT alone arms (4.3 months).

Summary and discussion

Whole brain radiotherapy alone versus whole brain radiotherapy plus stereotactic radiosurgery

There is class I evidence from two RCTs with similar inclusion criteria that single-dose SRS + WBRT provides significantly superior local tumor control compared with WBRT alone for patients with 1–3 brain metastases [25, 33] and evidence from one of the RCTs that this applies in patients with up to four brain tumors [25]. One of the RCTs also showed improved KPS score results for the single-dose SRS + WBRT regimen [33]. These results were achieved without an increased incidence of adverse therapeutic events [33]. While local control was a secondary endpoint, assessed post hoc in one of the RCTs [33], it was

the primary endpoint in the second [25], which confirmed the conclusion. Based on the inclusion criteria for both RCTs, a level 1 recommendation for single-dose SRS + WBRT would only have external validity for patients with a KPS $\geq$ 70.

There is class I evidence from one RCT that single-dose SRS + WBRT provides a significantly superior survival benefit compared with WBRT alone for patients with single brain metastases [33]. Once again, a level 1 recommendation reflecting a survival advantage in this setting for single-dose SRS + WBRT would only have external validity for patients with a KPS $\geq$ 70.

Whether or not a survival advantage might also exist for patients with $\geq$2 brain metastases remains controversial. Local tumor control is often assumed to dictate survival in a disease where 50% of patients die a neurological death with WBRT alone. It can be argued that one of the two RCTs was affected by excessive bilateral cross over (especially in the 2–3 tumor patient group) confounding the intent-to-treat survival analysis for patients with 2–3 tumors, while the second RCT, using local control as the primary endpoint, was stopped at too low a power to statistically prove a survival advantage in patients with 1–4 brain metastases. Certainly, the one class II evidence study that includes patients with 1–6 metastases [36] as well as the single class III evidence study [34] consistently support a significant survival advantage for single-dose SRS + WBRT in patients with multiple metastatic brain tumors. Nevertheless, a survival advantage for patients with 2–4 tumors has yet to be proven at the class I evidence level, and at most a qualified level 2 recommendation can be supported.

One class II study [36] and one class III study [34], each found a survival advantage for SRS + WBRT vs. WBRT alone for patients with a KPS $<$ 70, irrespective of brain tumor number, so long as all tumors were treated. The four arm retrospective cohort study by Wang et al. [36] included patients with 1–6 brain metastases and KPS scores of 40–90. Unfortunately the KPS score distributions were not stratified by treatment group for comparison purposes. The Sanghavi et al. [37] retrospective cohort study compared against the RTOG database and stratified by RPA classification is a much better designed study, but only rises to the class III evidence level. At most, the evidence supports a qualified level 3 recommendation regarding a survival advantage for SRS + WBRT over WBRT alone for patients with a KPS $<$ 70.

Stereotactic radiosurgery alone versus whole brain radiotherapy plus stereotactic radiosurgery

One RCT [38], one prospective cohort study (class II evidence) [35], and eight of 10 retrospective cohort studies (class II evidence) [40, 42–48] support equivalent survival results for single-dose SRS alone vs. WBRT + single-dose SRS, and one study restricted to breast cancer suggested a survival advantage for the single-dose SRS alone strategy [41]. Only one retrospective cohort study showed a survival result favoring WBRT + single-dose SRS, and this study was unusual in that it only included patients who had already survived >1 year since initial treatment [48].

Regarding local recurrence risk, the RCT [38] as well as 1/10 retrospective cohort studies [48] demonstrated that a single-dose SRS alone strategy led to a higher risk of local recurrence at the treated site compared with WBRT + single-dose SRS. A third study (second retrospective cohort study) reported an increased 1 year local recurrence rate (22 vs. 6%) but did not report statistical analysis [44]. In contrast, the prospective cohort study [35] as well as 6/10 retrospective cohort studies [36, 41–43, 45, 46] showed no significant difference in local recurrence risk at the treated site between the two treatment strategies. Clearly there exists conflicting data regarding the risk of local recurrence at the treated site if single-dose SRS is utilized in isolation. This conflicting evidence suggests that further study may be needed to define optimal dose prescription and/or dose rate for isolated SRS as opposed to SRS performed in the setting of an additive WBRT dose.

Three class I studies have demonstrated that WBRT lowers the risk of distant recurrence compared to local tumor therapies (SRS or surgical resection) used in isolation [15, 38, 57]. There is, however, disagreement among class I and II studies regarding the risk of distant recurrence outside the treatment volume if single-dose SRS is used in isolation as opposed to WBRT + single-dose SRS. The RCT [38], as well as 4/10 retrospective cohort studies [40, 42, 44, 45], demonstrated a significantly increased risk of either distant brain or overall brain recurrence when single-dose SRS is utilized in isolation and no advantage to SRS alone when assessing neurocognitive sequelae from radiation. The prospective cohort study [35] as well as 2/10 retrospective cohort studies [36, 47] did not assess the distant recurrence rate. Four of 10 retrospective cohort studies, however, revealed no significant difference in the distant recurrence rate between the two treatment strategies [41, 43, 46, 48]. Given the above results, prudence warrants regular careful surveillance at 2–3 month intervals with neuro-imaging if single-dose SRS is utilized in isolation.

An area that has not been fully studied to date includes the potential neuropsychological effects of adding WBRT to a SRS treatment regimen vs. the potential adverse neurocognitive effects of a potentially greater risk of recurrence outside the SRS site. Assessing functional status outcomes using standard functional scores tends to be insensitive to subtle neurocognitive effects. Even the MMSE is likely to be too crude a measure to assess the

neurocognitive parameters of interest to physicians and patients. Thus, a careful surveillance imaging strategy, if SRS is utilized in isolation, should be validated for both efficacy and for preserving neurocognitive function. While outside the specific search criteria for this chapter, limited evidence to date suggests that tumor recurrence is also associated with neurocognitive decline and thus may be taken into consideration when deciding to forego up-front WBRT. The potential differential neurocognitive consequences between these two therapeutic choices (SRS alone vs. SRS + WBRT) have not been well studied and remain uncertain, even if a careful surveillance strategy is implemented when SRS is used in isolation.

Stereotactic radiosurgery alone versus whole brain radiotherapy alone

The four class II evidence studies evaluating this comparison all demonstrated a statistically significant survival advantage for single-dose SRS alone compared with WBRT alone for patients with either single or multiple brain tumors [35, 36, 49, 50]. However, one study was confounded by the inclusion of SCLC patients who are normally excluded from solid metastatic brain tumor analysis, particularly in a study in which WBRT is not included in one of the arms [35]. A second study included a very small number of patients and was limited by selective rare histology (epithelial ovarian cancer only), and poor intergroup comparative analysis [49]. Consistent with these results, one class III evidence study showed a significant survival advantage for single-dose SRS alone for RPA class I and II, but not RPA class III patients [52]. Only one class III evidence study showed similar survival results for both treatment strategies [51]. While different studies evaluated patients with differing numbers of brain metastases, all studies included patients with up to three metastatic brain tumors. Given the relative paucity and weakness of the data, and despite relatively consistent results, only a level 3 recommendation is warranted.

Stereotactic radiosurgery plus WBRT versus resection plus WBRT

Of the four retrospective cohort trials evaluating this comparison, three demonstrated no significant survival differences between the two strategies [54–56]. Of these, two showed a trend favoring single-dose SRS + WBRT [54, 56] and one a trend favoring resection + WBRT [55]. Only one of the studies demonstrated a significant survival advantage for resection + WBRT [51]. This study reported SRS + WBRT results far worse than those reported by most studies using this strategy, both in terms of per survival results as well as excessive therapeutic toxicity and had poor enough internal validity that our writing group favored down-grading it from class II to class III evidence [53]. As further outlined and discussed in the surgical resection practice guideline of this series for brain metastases, these results suggest equivalence in survival results and a level 2 recommendation is consistent between the two guideline papers.

Stereotactic radiosurgery alone versus resection plus WBRT

One class I evidence study evaluating this comparison revealed no significant difference in functional performance outcome, neurological death outcome or median survival for patients with single brain metastases [57]. However, this study was closed prematurely with only 25% patient accrual for a study originally designed to detect a 15% difference in survival between the two groups. The revised statistical power calculation based on actual accrual data was designed to detect a survival difference of 38% or more in favor of surgery with 80% power (in accordance with a scenario retrospectively described by Bindal et al. in 1996). The actual sample size was large enough to reject the Bindal hypothesis concerning the overwhelming impact of surgery and in fact, revealed no significant difference between the two groups.

Of the three class II evidence studies evaluating this comparison, two revealed no significant difference in median survival for patients with 1–3 brain metastases [59, 60]. One suggested a trend favoring single-dose SRS alone for patients with 1–3 tumors [59], while the other suggested a trend favoring resection + WBRT for patients with single metastatic tumors [60]. The third study demonstrating a significant survival advantage for resection + WBRT or local RT was confounded by poor comparability among patient treatment arms with the SRS alone arm containing more than twice the percentage of multiple metastatic brain tumor patients than the resection + RT arm [60].

While the result for this comparison is one of the most eagerly anticipated in neuro-oncology, the current power flaws for the only class I evidence study, as well as the relative paucity, weakness, and conflicting results among other published evidence at most supports a level 3 recommendation for SRS in lieu of resection + WBRT.

Other comparisons

The absent and/or severely limited evidence (number as well as quality of studies) so far published in peer review literature does not yet support any clinical practice parameter guideline recommendations regarding:

1. The effectiveness of resection + single-dose SRS vs. resection + WBRT for patients with one or more solid brain metastases.
2. The effectiveness of substituting 2–5 dose SRS, or even 6–9 dose FSR, for single-dose SRS evaluated in the comparisons above and reflected in the clinical practice parameter guideline recommendations.
3. The effectiveness of substituting local RT for WBRT in the comparisons above and reflected in the clinical practice parameter guideline recommendations.

Key issues for further investigation

1. The potential survival advantage of single-dose SRS + WBRT for patients with ≥2 metastatic brain tumors <3 cm in diameter remains controversial and warrants further investigation with a RCT designed for sufficient statistical power for these patients with median survival as the primary endpoint.
2. The potential survival advantage of single-dose SRS + WBRT for patients with a KPS < 70 warrants further investigation in the form of a RCT.
3. The local control advantage of single-dose SRS for patients with ≥4 metastatic brain tumors and a KPS ≥ 70 warrants further investigation in the form of a RCT.
4. The optimal dose and/or dose rate for single-dose SRS utilized in isolation for treating metastatic brain tumors in order to ensure equivalent local recurrence rates compared with current single dose SRS + WBRT doses warrants further study.
5. The neurocognitive effects of SRS alone with careful neuroimaging follow-up leading to potential salvage SRS if recurrence develops, vs. SRS + WBRT, warrants further study with appropriate validated neurocognitive instruments and endpoints.
6. Based on current evidence classifications, single-dose SRS + WBRT vs. resection + WBRT warrants investigation in the form of a RCT.
7. Single-dose SRS alone vs. resection + WBRT warrants further investigation in the form of either a prospective cohort study or a RCT.
8. Resection + single-dose SRS vs. resection + WBRT warrants further investigation in the form of either a prospective cohort study or a RCT.
9. 2–5 dose SRS is relatively unproven in any of the comparison paradigms discussed in this paper. Clinical trials of 2–3 dose SRS vs. single-dose SRS are needed for all treatment comparisons outlined in this paper in either the form of prospective cohort studies or RCTs.
10. The effectiveness of local RT is relatively unproven compared with WBRT in any of the comparison paradigms discussed in this paper. Clinical trials of local RT vs. WBRT are most needed for settings of limited CNS disease where treatment strategies are designed to maximize local control (e.g., SRS + local RT vs. SRS + WBRT or resection + local RT vs. resection + WBRT).

The following is a list of major ongoing randomized trials pertaining to the use of stereotactic radiosurgery that evaluate treatment comparisons addressed by this guideline paper for the management of newly diagnosed brain metastases.

1. Randomized trial comparing radiosurgery with vs without whole brain radiotherapy
   Official title: A phase III prospective randomized trial comparing radiosurgery with versus without whole brain radiotherapy for 1–3 newly diagnosed brain metastases
   Status: Active, not recruiting (Phase III)
   Clinicaltrials.gov Identifier: NCT00548756
   Principal Investigator: Eric L. Chang, MD, U.T.M.D. Anderson Cancer Center
   Location: United States
   Sponsors and Collaborators: M.D. Anderson Cancer Center
2. Stereotactic radiation therapy with or without whole-brain radiation therapy in treating patients with brain metastases
   Official title: Phase III randomized trial of the role of whole brain radiation therapy in addition to radiosurgery in patients with one to three cerebral metastases
   Status: Recruiting (Phase III)
   Clinicaltrials.gov Identifier: NCT00377156
   Principal Investigators:
   Study Chair: Paul D. Brown, MD Mayo Clinic
   Investigator: Kurt A. Jaeckle, MD Mayo Clinic
   Investigator: Richard L. Deming, MD Mercy Therapeutic Radiology Associates, PC at Mercy Medical Center - Des Moines
   Investigator: Elana Farace, PhD Milton S. Hershey Medical Center
   Investigator: Bruce Pollock, MD Mayo Clinic
   Study Chair: Anthony Asher, MD, FACS Carolina Neurosurgery and Spine Associates
   Investigator: Fred G. Barker, MD Massachusetts General Hospital
   Study Chair: Larry Kleinberg, MD Sidney Kimmel Comprehensive Cancer Center
   Study Chair: Anthony Asher, MD, FACS Carolina Neurosurgery and Spine Associates
   Location: United States and Canada (38 locations)
   Sponsors and Collaborators:
   North Central Cancer Treatment Group

National Cancer Institute (NCI)
American College of Surgeons
Eastern Cooperative Oncology Group
Radiation Therapy Oncology Group

3. Surgery versus stereotactic radiosurgery in the treatment of single brain metastasis: a randomized trial
Official title: Surgery versus stereotactic radiosurgery in the treatment of single brain metastasis: a randomized trial
Status: Completed
Clinicaltrials.gov Identifier: NCT00460395
Principal Investigator: Frederick F. Lang, M.D., University Of Texas MD Anderson Cancer Center
Location: United States
Sponsors and Collaborators: M.D. Anderson Cancer Center
4. Surgery versus radiosurgery to treat metastatic brain tumors
Official title: A prospective, randomized trial comparing surgery versus radiosurgery for the treatment of metastatic brain tumors
Status: Completed
Clinicaltrials.gov Identifier: NCT00075166
Location: United States
Sponsors and Collaborators: National Institute of Neurological Disorders and Stroke (NINDS)
5. A trial of postoperative whole brain radiation therapy vs. salvage stereotactic radiosurgery therapy for metastasis
Official title: Randomized phase III trial of postoperative whole brain radiation therapy compared with salvage stereotactic radiosurgery in patients with one to four brain metastasis: Japan Clinical Oncology Group Study (JCOG 0504)
Status: Recruiting (Phase III)
Clinicaltrials.gov Identifier: NCT00280475
Principal Investigator: Takamasa Kayama, MD, PhD Yamagata University Faculty of Medicine
Location: Japan (21 locations)
Sponsors and Collaborators:
Japan Clinical Oncology Group
Japanese Ministry of Health, Labor and Welfare
6. A trial comparing radiosurgery with surgery for solitary brain metastases
Official title: A randomised trial of surgery plus whole brain radiotherapy (WBRT) versus radiosurgery plus WBRT for solitary brain metastases
Status: Recruiting (Phase III)
Clinicaltrials.gov Identifier: NCT00124761
Principal Investigator: Daniel Roos, FRANZCR, Royal Adelaide Hospital
Location: Australia
Sponsors and Collaborators: Royal Adelaide Hospital
7. Adjuvant radiation therapy in treating patients with brain metastases
Official title: Phase III trial on convergent beam irradiation of cerebral metastases
Status: Active, not recruiting (Phase III)
Clinicaltrials.gov Identifier: NCT00002899
Principal Investigators:
Rolf-Peter Mueller, MD Medizinische Universitaetsklinik I at the University of Cologne
Riccardo Soffietti, MD Universita Degli Studi di Turin
Location: Europe (33 locations)
Sponsors and Collaborators: European Organization for Research and Treatment of Cancer

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Disclaimer of liability The information in these guidelines reflects the current state of knowledge at the time of completion. The presentations are designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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