

REVIEW

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# Stereotactic radiosurgery (SRS) for brain metastases: a systematic review

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## Abstract

In many patients with brain metastases, the primary therapeutic aim is symptom palliation and maintenance of neurologic function, but in a subgroup, long-term survival is possible. Local control in the brain, and absent or controlled extracranial sites of disease are prerequisites for favorable survival. Stereotactic radiosurgery (SRS) is a focal, highly precise treatment option with a long track record. Its clinical development and implementation by several pioneering institutions eventually rendered possible cooperative group randomized trials. A systematic review of those studies and other landmark studies was undertaken. Most clinicians are aware of the potential benefits of SRS such as a short treatment time, a high probability of treated-lesion control and, when adhering to typical dose/volume recommendations, a low normal tissue complication probability. However, SRS as sole first-line treatment carries a risk of failure in non-treated brain regions, which has resulted in controversy around when to add whole-brain radiotherapy (WBRT). SRS might also be prescribed as salvage treatment in patients relapsing despite previous SRS and/or WBRT. An optimal balance between intracranial control and side effects requires continued research efforts.

**Keywords:** Brain metastases, Radiation treatment, Radiotherapy, Stereotactic radiosurgery

Historically, treatment options for patients with brain metastases from solid tumors were limited to surgery and/or whole-brain radiotherapy (WBRT) supported by corticosteroids if indicated, with few systemic therapies available that were able to impact on extracranial metastases. Therefore, median survival after non-surgical management typically was in the range of 3-4 months [1]. Both intra- and extracranial disease progression was common, resulting in complex clinical situations with components of decreasing performance status (PS), neurological status, and impaired organ function, e.g. from liver and lung metastases. Few patients who relapsed in the brain received salvage treatment such as reirradiation [2,3]. Partial brain fields or repeat WBRT were available but the efficacy of these salvage attempts was modest [4]. There was an urgent need for new treatment approaches, and among several avenues of research, clinical implementation of single fraction stereotactic radiosurgery (SRS) during the 1980s probably was the single most important innovation. The neurosurgery field gets credit for the

early exploration of SRS [5-7], but the evolution of imaging, radiation treatment planning and delivery technology had to occur before several dedicated research groups were able to safely deliver SRS to patients with brain metastases [8-11]. The present review, which is based on a well defined method for identification of relevant studies, focuses on recent developments.

## Methods

A systematic search of the citation database Scopus (Elsevier B.V., www.scopus.com) by use of the terms 'stereotactic AND brain' and 'radiosurgery' was performed on 17<sup>th</sup> January 2014. We did not use more specific search terms in order to avoid missing relevant publications. Articles were selected irrespective of language, year of publication and article type (review, guideline, clinical study, experimental study etc.), as described previously [12]. In order to determine whether or not a given article reported on SRS for brain metastases we accessed its abstract. Then, all articles dealing with the subject of this review were ranked by number of citations (field 'times cited' in the Scopus citation database) in order to create a list of articles with the highest number of citations, referred to as landmark studies (list available on

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request from the corresponding author). The top 50 articles were reviewed for contents, study type (phase I, II, III, retrospective etc.) and outcomes. Given that such hitlists are dominated by older publications because recent articles are less likely to have accumulated high numbers of citations [13], separate searches were performed that covered the years 2011 and 2012, respectively. The authors also used their reference lists from previous reviews [14-17] to cross-check for important studies that might not have been cited as often as expected. In addition, on 22<sup>nd</sup> March 2014 the database Medline/PubMed was searched by the two terms mentioned above.

## Results and discussion

Table 1 contains the 25 most-cited articles [18-42]. These were published between 1990 and 2010. Of these, the prospective randomized clinical trials acquired the highest numbers of citations per year [18-20]. Most clinically relevant aspects of SRS for brain metastases are represented in the table, including the role of SRS alone compared to

SRS plus WBRT, the role of WBRT alone compared to WBRT plus SRS, the role of SRS compared to surgery, patient selection based on prognostic models, SRS for recurrent disease, radiobiology of SRS, and toxicity. Issues related to the outcomes of different treatment planning approaches and treatment units ranked among the top 50 rather than the top 25 articles [10,43-66]. The most cited publications from the year 2011 did not cover any new aspects [67-71]. However the 2012 articles focused on new topics such as SRS to resection cavities in the postoperative setting, SRS in patients with more than 4 brain metastases, and new systemic treatments in addition to SRS [72-76]. Fractionated stereotactic radiotherapy was not among the most-cited topics.

We will not discuss postoperative SRS in great detail, because this investigational approach so far is not yet supported by randomized trials [76]. Phase 2 data suggests that postoperative SRS is associated with high rates of local control, especially for non-superficial brain metastases of limited size (<3 cm) [77]. Metastases  $\geq 3$  cm

**Table 1 Articles with most citations (ranked by absolute count)**

<i>Authors and year of publication</i>	<i>Study description</i>	<i>Absolute citation count</i>	<i>Citations per year</i>
Andrews et al. 2004 [18]	RTOG 9508 randomised trial	812	81
Aoyama et al. 2006 [19]	SRS $\pm$ WBRT randomised trial	527	66
Kondziolka et al. 1999 [20]	WBRT $\pm$ SRS randomised trial	517	37
Flickinger et al. 1994 [21]	SRS for solitary BM, multi institutional	445	22
Shaw et al. 2000 [22]	RTOG protocol 90-05	393	28
Alexander et al. 1995 [23]	Retrospective study	377	21
Auchter et al. 1996 [24]	SRS for resectable single BM, multi institutional	344	20
Chang et al. 2009 [25]	SRS $\pm$ WBRT randomised trial	314	63
Sneed et al. 2002 [26]	SRS $\pm$ WBRT, multi institutional	286	26
Sneed et al. 1999 [27]	SRS $\pm$ WBRT, single institution	286	20
Pirzkall et al. 1998 [28]	SRS $\pm$ WBRT, single institution	229	15
Sperduto et al. 2008 [29]	Prognostic score, incl. RTOG 95-08 data	216	36
Mehta et al. 1992 [30]	Prospective single arm, n = 40	186	9
Bindal et al. 1996 [31]	SRS vs. resection	182	10
Engenhart et al. 1993 [32]	Retrospective study	178	9
Mori et al. 1998 [33]	SRS for melanoma BM	169	11
Hall & Brenner 1993 [34]	Radiobiology of SRS	169	8
Shiau et al. 1997 [35]	Local control after SRS	165	10
Aoyama et al. 2007 [36]	Neurocognitive outcome, randomised trial	163	23
Muacevic et al. 1999 [37]	SRS vs. resection	163	11
Chao et al. 2001 [38]	Radionecrosis vs. relapse after SRS	161	12
Adler et al. 1992 [39]	Retrospective study	161	8
Sanghavi et al. 2001 [40]	Multi institutional, stratified for prognosis	156	12
Sperduto et al. 2010 [41]	Prognostic score, diagnosis specific	155	39
O'Neill et al. 2003 [42]	SRS vs. resection	155	14

RTOG: Radiation Therapy Oncology Group, SRS: stereotactic radiosurgery, WBRT: whole-brain radiotherapy, BM: brain metastases.

with superficial dural/pial involvement demonstrated the highest risk of local failure. In a different study, patients with breast cancer had the highest risk of leptomeningeal progression following SRS (24% at 1 year) [78]. Head to head comparisons of SRS to other types of postoperative radiotherapy, including WBRT, are needed to conclusively evaluate the pros and cons of SRS in this setting.

Some institutions have more than 25 years of experience with SRS and have collected data on thousands of patients, often transferred to multi institutional databases. A recent Japanese multi institutional prospective study included 1194 patients (76% with lung cancer) [79]. Its aim was to examine whether survival after SRS without WBRT as initial treatment for patients with 5-10 brain metastases (median 6) was non-inferior to that of patients with 2-4 lesions. Size limits were metastases <3 cm in longest diameter, largest tumor <10 ml in volume, and total cumulative volume ≤15 ml. Median survival was longest in patients with one lesion (n = 455, 13.9 months). But patients with 2-4 lesions had comparable survival to patients with 5-10 lesions (median survival 10.8 months, hazard ratio 0.97, 95% confidence interval 0.81-1.18). This met the pre-specified definition of non-inferiority, despite the development of new lesions in >60% of patients. Further salvage SRS was done in more than 40%, and 9% received salvage WBRT. The delivery of further SRS or WBRT was not significant different between the groups. Grade 3-4 adverse events occurred in up to 3% of patients in each group. Only 8% of patients died from their brain disease.

As displayed in Table 2, SRS achieves high rates of local progression-free survival of SRS-treated lesions and its efficacy may be less influenced by histology or radiosensitivity than that of fractionated radiotherapy [63]. At the same time, severe complications are observed in a minority of patients. This is the primary reason for many institutions to expand its utilization beyond the initial target population, which often was defined as those with 1-3 lesions. The Japanese study [79] suggests that SRS is

reasonable for patients with up to 10 lesions. However, it is also known that number of initial lesions predicts the risk for development of new metastases and thus need for salvage treatment (new course of SRS or WBRT). Primary tumor type and extracranial disease status also impact on distant brain failure risk. Based on these three predictors, a nomogram was recently developed (n = 464 patients) [80]. Table 3 shows examples calculated according to this model, which should be validated further.

Post-SRS adjuvant WBRT reduces intracranial relapses and neurologic deaths but fails to improve the duration of functional independence and overall survival [67,84]. The major obstacle against the general adoption of combined SRS and WBRT is the fear of neurocognitive decline after WBRT. Patients with limited survival expectation because of progressive, uncontrollable extracranial disease should be managed with WBRT or best supportive care rather than SRS [85,86].

#### First line SRS and the controversy around whole-brain radiotherapy

Focal treatment such as SRS, improves the local control observed with WBRT. In a small randomized study primarily addressing this endpoint, patients with 2-4 brain metastases (all ≤25 mm diameter) either received WBRT alone (30 Gy in 12 fractions) or WBRT plus SRS [20]. The study was stopped at an interim evaluation following accrual of just 27 patients. The rate of local failure at 1 year was 100% after WBRT alone but only 8% in patients who had boost SRS. In exploratory analysis, patients who received WBRT alone lived a median of 7.5 months, while those who received WBRT plus RS lived 11 months (p = 0.22). With only 27 patients, possible survival differences cannot be adequately assessed. A different randomized study by the Radiation Therapy Oncology Group (RTOG) enrolled 333 patients with 1-3 brain metastases [18]. Maximum diameter of the largest lesion was 4 cm and additional lesions could not exceed 3 cm. Minimum

**Table 2 Results of stereotactic radiosurgery (SRS) for brain metastases**

Reference	n (patients/lesions)	Prescribed dose (median; range [Gy])*	Median OS (m)	1-year PFS (%)
Pirzkall et al. 1998 [28]	236/311	20; 10-30	5.5	89
Cho et al. 1998 [81]	73/136	17.5; 6-50	7.8	80
Sneed et al. 1999 [27]	62/118 <sup>a</sup>	18; 15-22	11.3	80
	43/117 <sup>b</sup>	17.5; 15-22	11.1	86
Varlotto et al. 2003 [82]	137/208	16; 12-25	Not given	90
Andrews et al. 2004 [18]	164/269 <sup>c</sup>	Not given; 15-24	6.5	82
Bhatnagar et al. 2006 [83]	205/4-18 lesions each <sup>d</sup>	16; 12-20	8.0	71

OS: overall survival in months; PFS: progression-free survival.

\*Prescription isodose or point varied, some series included SRS plus WBRT.

<sup>a</sup>SRS only.

<sup>b</sup>SRS plus WBRT (no significant difference in OS and PFS between both groups).

<sup>c</sup>SRS plus WBRT.

<sup>d</sup>SRS plus/minus WBRT.

**Table 3 Estimates of 6-month survival without distant brain failure based on a new nomogram [80]**

Primary tumor type	1-3 BM, stable systemic disease	1-3 BM, progressive systemic disease	4-13 BM, stable systemic disease	4-13 BM, progressive systemic disease
Renal cell cancer	69%	67%	48%	46%
Malignant melanoma	57%	55%	32%	30%
Lung, adeno ca	74%	72%	55%	53%
Lung, squamous ca	58%	57%	33%	32%
Breast, Her-2 positive	73%	72%	53%	52%
Breast, Her-2 negative	67%	66%	43%	42%

Sex, age and race impact slightly on failure risk. The examples refer to approximately 55-60 years-old Caucasian females. The differences for male patients are in the order of 1-2%.

BM: brain metastases.

Karnofsky PS was 70. WBRT dose was 37.5 Gy in 15 fractions in both groups. SRS boost dose was adjusted to lesion size (24 Gy, 18 Gy and 15 Gy for lesions < 2 cm, > 2 cm but less than 3 cm, and > 3 cm but < 4 cm, respectively). Median survival was significantly better after SRS boost in patients with single brain metastasis. By multivariate analysis, survival was also improved in recursive partitioning analysis (RPA) class I patients (RPA details are provided in Table 4). SRS-treated patients were more likely to have a stable or improved PS at 6 months (43% vs 27%,  $p = 0.03$ ). Central imaging review showed higher response rates at 3 months and better control of the treated lesions at 1 year,  $p = 0.01$ . The risk of developing a local recurrence was 43% greater with WBRT alone. The addition of temozolomide or erlotinib did not improve survival after WBRT and SRS in another randomized RTOG trial, which included only patients with non-small cell lung cancer [87].

After many years of controversy about the role of combining WBRT with SRS and considerable variation in practice [27,28], a Japanese group completed a prospective randomized multicenter phase III study of SRS alone vs combined SRS and WBRT [19]. The primary endpoint was survival with an expected difference of 30%. The trial included adult patients with Karnofsky PS >60 and a

maximum of 4 brain metastases, none exceeding 3 cm diameter. The patients were stratified by number of lesions (1 vs 2-4), extracranial tumor activity (active vs stable, i.e. controlled for at least 6 months), and primary tumor (lung cancer vs others). WBRT was given in 10 fractions of 3 Gy. SRS dose varied with size of the lesion (up to 2 cm: 22-25 Gy, > 2 cm: 18-20 Gy margin dose), and was reduced by 30% if WBRT was given. The mean dose was 21.9 Gy in the SRS alone arm and 16.6 Gy in the combined arm. The combined arm contained 65 patients, the SRS arm 67 patients. Almost 50% of patients had a single lesion. The SRS group contained slightly more patients with PS 90-100% (66 vs 52%) and patients without neurological symptoms (70 vs 59%). However, the differences were not statistically significant. Median survival was 7.5 months after SRS plus WBRT and 8 months after SRS alone. One-year survival in the combined treatment arm was increased by 36%, but was not statistically significantly different, possibly due to low patient numbers (38.5 vs 28.4%,  $p > 0.05$ ). There was no significant difference in the percentage of patients that died from predominantly neurologic causes (23 vs 19%). Age, PS, extracranial disease activity and status of the primary tumor were significant prognostic factors on multivariate analysis. After SRS alone, 2 patients developed serious late complications

**Table 4 Prognostic value of recursive partitioning analysis (RPA) classes**

Reference	Number of patients	RPA class I	RPA class II	RPA class III
Gaspar et al. 1997 [88]	1200	7.1	4.2	2.3
Lorenzoni et al. 2004 [89]	110 (SRS)	27.6	10.7	2.8
Franzin et al. 2009 [90]	185 (SRS)	17.0	10.0	3.0
Likhacheva et al. 2012 [91]	251 (SRS)	38.8	9.4	2.8
Zindler et al. 2013 [92]	380 (SRS)	18.0*	10.0*	4.0*
Sneed et al.	268 (SRS)	14.0	8.2	5.3
2002 [26]	301 (SRS + WBRT)	15.2	7.0	5.5

Median survival in months from different publications.

RPA class I: age <65 years, Karnofsky performance status  $\geq 70$ , controlled primary tumor, no extracranial metastases.

RPA class II: all other patients.

RPA class III: Karnofsky performance status <70.

SRS: stereotactic radiosurgery, WBRT: whole-brain radiotherapy.

\*estimated from Kaplan-Meier graphs included in the publication.

(radionecrosis and grade 4 seizures, respectively). After SRS plus WBRT, 3 patients developed a radionecrosis and 3 signs of leukencephalopathy. The rate of actuarial failure at 1 year was 47% after combined treatment, but significantly greater at 76% after SRS alone (relative increase of 62%;  $p < 0.001$ ). New lesions developed in 42 vs 64% ( $p = 0.003$ ). The risk was significantly higher in patients presenting with 2-4 lesions before treatment, those with active extracranial metastases and those with PS 70-80. WBRT reduced the risk of failure at the site of SRS from 27% to 11% after one year ( $p = 0.002$ ).

The highly cited randomized trial from the M.D. Anderson Cancer Center re-emphasized patient selection issues as critical for overall survival [25]. In this trial, patients with 1-3 newly diagnosed brain metastases were randomly assigned to SRS plus WBRT or SRS alone, and over an almost 7-year time frame, 58 patients were recruited and stratified by RPA class, number of brain metastases, and histology. The primary endpoint was neurocognitive function: measured as a 5-point drop compared with baseline in the Hopkins Verbal Learning Test-Revised (HVLRT-R) total recall at 4 months. An interim analysis showed that there was a high probability (96%) that patients assigned to receive SRS plus WBRT were more likely to show a decline in learning and memory function at 4 months than patients assigned to receive SRS alone. Further, at 4 months there were four deaths (13%) in the group that received SRS alone, and eight deaths (29%) in the group that received SRS plus WBRT, and 73% of patients in the SRS plus WBRT group were free from CNS recurrence at 1 year, compared with 27% of patients who received SRS alone ( $p = 0.0003$ ). These differences in early death bring into question the generalizability of the HVLRT-R score results. It is well known that a general disease-related decline due to progression, especially in the pre-terminal phase will cause a significant drop in neurocognitive function, and its attribution to a single component, such as WBRT can be misleading. Another potential confounder in evaluating survival following SRS, with or without WBRT, is the initiation of systemic treatment after radiation. Moreover, several drug regimens are known to impact on brain function [93]. Ongoing studies evaluate hippocampal sparing WBRT, which aims at reducing dose to critical structures and thereby risk of function decline, while maintaining improved brain control [94,95]. In many clinical scenarios, acceptable approaches include SRS or SRS plus WBRT, as also summarized in an American Society for Radiation Oncology (ASTRO) guideline [14] and recent reviews [84,96].

#### **Salvage SRS as reirradiation after whole-brain radiotherapy**

The potential advantages of SRS as salvage treatment after WBRT were realized early during the development of SRS

[97]. The RTOG completed a prospective phase 1 clinical trial (RTOG 90-05) of SRS in recurrent, previously irradiated primary brain tumors and brain metastases. This was a dose escalation trial, which included 100 patients with brain metastases after prior WBRT to a median dose of 30 Gy [22]. Eligible patients had received first-line radiotherapy at least 3 months prior to study entry, and in the study, the actual median interval was 17 months. Life expectancy was  $\geq 3$  months. Seventy-eight percent of patients had single lesions. Dose was determined by the maximum diameter of the tumor. Initial doses were 18 Gy for lesions  $\leq 20$  mm, 15 Gy for lesions measuring 21-30 mm, and 12 Gy for lesions measuring 31-40 mm. Dose was prescribed to the 50-90% isodose line, which was to encompass the entire enhancing target volume. The dose was escalated in 3 Gy increments providing there was not an excess of unacceptable toxicity. The trial eventually defined the maximum acutely tolerable SRS dose in this setting, except for lesions  $\leq 20$  mm where the dose was not escalated beyond 24 Gy because of investigators' reluctance. While small lesions  $\leq 20$  mm can be treated with up to 24 Gy to the margin of the lesion, those that measure between 21 and 30 mm might receive 18 Gy, and those that measure between 31 and 40 mm 15 Gy. Median survival was 7.5 months. Long-term toxicity data for 64 brain metastases patients revealed four patients developed radionecrosis requiring operation 5-14 months after SRS. This study therefore provides tentative evidence that retreatment with SRS can produce extended survival, but the incidence of necrosis must be factored in.

More recent data were derived from a retrospective review of 106 patients irradiated for a median of 2 metastases (range, 1-12) with a median dose of 21 Gy (range, 12-24) prescribed to the 50% isodose [98]. With a median follow-up of 10.5 months, local control was 83% at 6 months and 60% at 1 year. Median progression-free survival was 6.2 months. Median overall survival was 11.7 months from salvage SRS, and 22 months from initial diagnosis. Comparable outcomes were achieved in another retrospective series that included 111 patients [99]. SRS doses were usually prescribed according to the RTOG 90-05 guidelines. Median survival was 9.9 months. Twenty-five percent of patients developed further local progression in spite of salvage SRS. Poorer local control was observed in lesions  $> 2$  cm, which usually had been treated with lower radiation doses. Caballero et al. analyzed 310 patients [100]. The median number of brain metastases was 3, and interval from WBRT to SRS 8 months. The median survival was 8.4 months overall and 12.0 vs. 7.9 months for single vs. multiple lesions ( $p = 0.001$ ). There was no relationship between number of lesions and survival after excluding patients with single metastases. Retrospective population-based data from Canada suggested that salvage SRS after WBRT was not associated with compromised survival

compared to immediate boost SRS [101]. Only preliminary experience with small numbers of patients exists for salvage SRS after first-line SRS [102]. No definitive conclusions regarding long-term safety have yet been published.

### Prognostic staging systems

Patients with brain metastases have always presented with a variable spectrum of number, size and location of lesions, with different pattern and activity of extracranial disease, and with a wide range of comorbidities and PS. Estimation of prognosis is possible by using developed staging systems (Table 4) [41,43,88,89]. For example the RTOG developed the first RPA to define 3 classes of patients with statistically different predicted survival [88]. Other systems for predicting survival include the score index for radiosurgery (SIR) [43], basic score for brain metastases (BSBM) [89], and diagnosis-specific graded prognostic assessment (DS-GPA) score [41]. The latter is an increasingly used 4-tiered system that provides survival outcomes for patients with lung, breast, kidney and gastrointestinal cancers as well as malignant melanoma. These patients were treated with a variety of different approaches including but not limited to SRS. Their data were also used to create a prognostic nomogram [103]. In a recent study, symptomatic patients had an increased hazard for all-cause mortality (hazard ratio, 1.4) and were more likely to experience neurologic death after SRS (42% vs 20%,  $p < 0.0001$ ) [104]. Relative to asymptomatic patients, symptomatic patients required more craniotomies (43% vs 5%,  $p < 0.0001$ ) and were more likely to have RTOG grade 3 and 4 post-treatment symptoms (24% vs 5%;  $p < 0.0001$ ).

### Conclusions

SRS results in a high probability of treated-lesion control and, when adhering to typical dose/volume recommendations, a low normal tissue complication probability. However, SRS as sole first-line treatment carries a risk of failure in non-treated brain regions. SRS might also be prescribed as salvage treatment in patients relapsing despite previous SRS and/or WBRT. An optimal balance between intracranial control and side effects requires continued research efforts. Such efforts are also necessary to integrate new systemic treatments and/or stereotactic body radiotherapy, which aim at prolonged extracranial disease control.

### Competing interest

The authors declare that they have no competing interests.

### Authors' contributions

CN participated in the design of the study and extraction of the references. All authors helped to review the references and draft the manuscript. All authors read and approved the final manuscript.

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