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REVIEW

Frameless stereotactic radiosurgery for brain metastasis: a systematic review and meta-analysis

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Abstract

Stereotactic Radiosurgery (SRS) delivers a high dose of radiation to a specific brain area while limiting radiation to nearby healthy tissue. While most SRS has traditionally been performed with a stereotactic frame-based approach, this study aims to investigate the safety and efficacy of frameless radiosurgery in patients with brain metastases. Our study followed the recommended guidelines summarized in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. The electronic databases of PubMed/Medline, Scopus, Embase, and Web of Science (WOS) were searched from inception to 10 October 2023. The pooled rate of outcomes was calculated using random effect model and Restricted maximum–likelihood (REML) method. All statistical analysis was performed by STATA V.17. A total of 499 studies were recruited from the electronic databases. After removing duplicates ($n=117$), 382 studies were used for title/abstract, and 329 were removed from the study selection process. A total of 53 articles were used for full-text assessment, and 35 studies were included for data extraction. Our analysis revealed a significant increase across all pooled survival rates and local control rates by initiating the radiosurgery for patients, estimating the pooled 6-month OSR of 75% (95% CI: 68-81%), 1-year overall survival rate (OSR) of 60% (95% CI: 51-69%), 18-month OSR of 48% (95% CI: 10-85%), 2-year OSR of 39% (95% CI: 19-58%), 1-year progression-free survival rate (PFSR) of 68% (95% CI: 39-98%), 2-year PFSR of 75% (95% CI: 58-91%), 6-month local control rate (LCR) of 93% (95% CI: 90-96%), and 12-month LCR of 86% (95% CI: 82-90%). Our meta-analysis findings confirm the efficacy of frameless radiosurgery in treating brain metastases. Using data from several trials, we were able to demonstrate stereotactic radiosurgery's effectiveness as a therapy option for brain metastasis patients, demonstrating local control and reasonable overall survival.

Keywords Frameless · Stereotactic · Radiosurgery · Brain · Metastasis

Introduction

The most common type of brain tumor in adults is brain metastasis, accounting for 10–20% of all cancer patients and surpassing primary brain tumors by tenfold [1]. Lung, breast, melanoma, and kidney cancers account for most primary sites of brain metastases [2]. The symptoms include headaches, neurological deficits, and seizures. 40% of patients report headache as the first symptom, 15-20% have seizures, and 40% have localized neurological deficits such as hemianopsia, aphasia, and hemiparesis. Approximately 65% of patients suffer from cognitive impairment [3, 4].The number of brain metastases appears to have increased during the previous decade, regarding the utilization of magnetic resonance imaging (MRI), enhancement of therapeutic options for systematic disease, aging of the population, and the effectiveness of drugs that do not cross the blood-brain barrier [5–7]. The four main definitive therapies are whole-brain radiation therapy (WBRT), surgery, stereotactic radiosurgery (SRS), and medical therapy with chemotherapy, immunotherapy, or precision medicine approaches [8]. Young individuals with limited extracranial disease may benefit from surgical excision of a single brain metastasis, followed by radiosurgery for two to four metastases. The

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advantages of WBRT after surgery or radiosurgery remain uncertain. Thus, two therapies are available in patients with a favorable prognosis: WBRT after surgery or radiosurgery or observation with MRI follow-up [8].The use of SRS to treat brain metastases in patients has been on the rise. Multiple studies have shown its effectiveness when used alone or combined with WBRT [9–12]. Radiation therapy with SRS delivers a high dose of radiation to a specific area of an organ while limiting radiation to healthy tissue nearby [13]. An immobilizing head frame is used to immobilize the patient, and stereotactic coordinates target a specific area in the brain and enable precise immobilization and positioning accuracy of less than 1 mm during image capture and treatment [14]. There are several downsides to this intrusive technique, including discomfort and anxiety for the patient. The rigid head frame also requires the presence of a neurosurgeon during installation. Nevertheless, developments in computer engineering, radiologic technology, and radiological methods have offered the potential to transcend the constraints of traditional frames [15].In recent years, non-invasive frameless stereotactic systems have become preferred over traditional patient fixation methods. These frameless systems have shown positional accuracy within the 1–4 mm range, which may vary due to differences in patient fixation, positioning, and accuracy assessment methods [16, 17]. It is crucial to incorporate a small safety margin into the target volume to account for localization and set-up errors, which is essential for minimizing potential treatment-related complications of SRS. Furthermore, the volumes of normal brain tissue exposed to high radiation doses can indicate the development of brain radionecrosis. Studies suggest that brain radionecrosis can occur in up to 47% of treated lesions for brain volumes larger than ten cc receiving a dose of 12 Gy [18].In the current study, we aimed to explore the primary outcomes of frameless SRS, including overall survival (OS), progression-free survival (PFS), local control (LC), and radiological response, and secondary outcomes, including adverse radiation effects, further therapies, and radionecrosis for patients with brain metastases, which can assist neurosurgeons in treating these difficult patients.

Method

The study followed the recommended guidelines summarized in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [19].

Search strategy

An inclusive search was conducted thoroughly with relative keywords. Four online databases of PubMed/Medline, Scopus, Embase, and Web of Science (WOS) were surveyed until 2023 without any limitation. The search syntax included crucial keywords such as “brain”, “metastasis,”, “frameless”, and “radiosurgery”. For more features about the search methodology, please refer to the supplementary materials (Table S1).

Eligibility criteria

In this research, we utilized well-defined criteria for including or excluding to recruit the relevant studies. Moreover, we exploited the PICO structure as a systematic approach to guide our investigation. The inclusion criteria for this study were as follows:

1. English studies.
2. Studies conducted on human subjects with BM.
3. Studies used frameless radiosurgery as treatment.
4. Studies reported outcomes such as OS, PFS, and LC.
5. Original articles, cross-sectional studies, cohorts, case-control, and clinical trials.

The exclusion criteria for this study were as follows:

1. Non-English studies.
2. In vivo and in vitro studies.
3. Studies without BM confirmation or without employment of frameless radiosurgery as a treatment.
4. Lack of outcome.
5. Non-original articles such as Case reports/series, thesis, notes, conference abstracts, book chapters, letters, reviews, systematic reviews, and meta-analyses.

Study selection

The data attained from exploring each database was exported to the EndNote V.20 for a thorough screening process. Two independent reviewers managed the primary screening of initial records by removing duplicate articles from the study selection process. Then, the remaining studies underwent title/abstract screening, and the relevant studies went through a detailed evaluation, which was a full-text assessment. Afterward, studies that came to have the eligibility criteria were selected for data extraction and synthesis. In cases of a conflict, the disagreement was resolved by a third reviewer.

Data extraction

Two reviewers conducted the data extraction process to gather crucial information from the chosen studies. A third senior (MA.H) reviewer resolved the disagreements. The demographic characteristics of articles, characteristics of brain metastasis, SRS features, and outcomes were extracted. Also, pooled rates of OS, LC, and PFS were computed to represent the success of treatment. The complications of adverse radiation effects and radionecrosis were also investigated.

Data synthesis

To get the proper effect size, the Cochrane Handbook for Systematic Reviews of Interventions was used. The percentages of LC, OS, and PFS rates were pooled using a random effect model with a restricted maximum likelihood (REML) method. The Cochrane's Q and I^2 test was employed to assess heterogeneity. The heterogeneity was considered significant if $I^2 > 40\%$ and Q test P-value < 0.001. We performed a subgroup analysis to account for potential moderators. Each study's influence on the pooled estimates was determined using a sensitivity analysis with the leave-one-out meta-analysis. We examined to determine publication bias by funnel plot and ran regression-based Egger test. Statistical significance was considered as a p-value less than 0.05. All statistical analysis was done by STATA version 17.0 (Stata Corp, College Station, TX).

Quality assessment

The quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS). The NOS quality evaluation has three sections: selection, comparability, and exposure/outcome. Studies were grouped according to their overall score: 1–3 for low-quality research, 4–6 for intermediate-quality research, and 7–9 for high-quality research (Table S2).

Results

Study selection

Our exploration of various databases yielded 499 studies, from which 117 were excluded due to duplication. After the initial screening, 382 studies underwent title/abstract screening, which excluded 329 studies. Eventually, 53 studies underwent a full-text screening. Eighteen studies were excluded from the full-text assessment due to the non-English studies ($n=2$), wrong population ($n=5$), wrong design ($n=7$), and not reported outcome ($n=4$). Ultimately, 35 studies were included for data extraction and synthesis. The details of the whole study selection process are summarized and depicted in Fig. 1.

Baseline characteristics

We extracted data from 35 eligible studies with 2253 cancer patients with single or multiple brain metastasis from cancer of any histology who received disparate prescription doses and fractions of SRS. Four clinical trials accompanied by 26 retrospectives and four prospective cohorts, published between 2005 and 2022, were enrolled for evaluation. Most of the studies took place in the US (18), followed by Germany (6) and Italy (3). The participants' gender was reported in 31 studies ($n=2162$), while 1066 (49.3%) and 1096 (50.7%) were male and female, respectively. The mean age of the patients in the studies ranged from 49.5 to 67 years. Table 1 depicts the characteristics of the enrolled studies.

Brain metastasis characteristics

Thirty-two studies demonstrated the primary site of brain metastasis in the enrolled patients ($n=2079$), indicating 872 patients with lung cancer (41.9%), 353 with breast cancer (16.9%), 314 with melanoma (15.1%), 161 with gastrointestinal cancer (7.7%), 82 with renal cell carcinoma (RCC) (3.9%), 43 with adenocarcinoma (2%), 25 with gynecological cancer (1.2%), and 229 with other cancers (11%), as the most common primary sites. The mean number of brain metastasis in enrolled patients differed between 1 and 5; however, two studies reported an outranged mean number of 20 and 13 [35, 51]. Considering median tumor volume, 19 studies denoted a wide range from 0.11 to 19.53 cc. Eighteen studies reported the mean Karnofsky Performance Scale (KPS) Score of the patients, which ranged from 50 to 100%. The RPA classification was surveyed, and most of the patients had an RPA class II (0.69 [95%CI:0.61–0.78]), RPA class I (0.19 [95%CI:0.13–0.24]), and RPA class III (0.11 [95%CI:0.06–0.16]), retrospectively.The location of the tumor was also investigated, and analysis showed that the frontal lobe (0.23 [95%CI:0.17–0.29]) was the most common location followed by the parietal lobe (0.21 [95%CI:0.18–0.23]), cerebellar (0.18 [95%CI:0.13–0.22]), temporal (0.17 [95%CI:0.14–0.19]), occipital (0.12 [95%CI:0.09–0.15]), and brainstem (0.05 [95%CI:0.00-0.09]), retrospectively.

24 studies reported prior treatments, including WBRT ($n=371$), chemotherapy ($n=262$), surgery ($n=92$), hormone therapy ($n=14$), immunotherapy ($n=12$), and targeted therapy ($n=8$). In addition, we identified 30 patients who received WBRT following radiosurgery (Table 2).

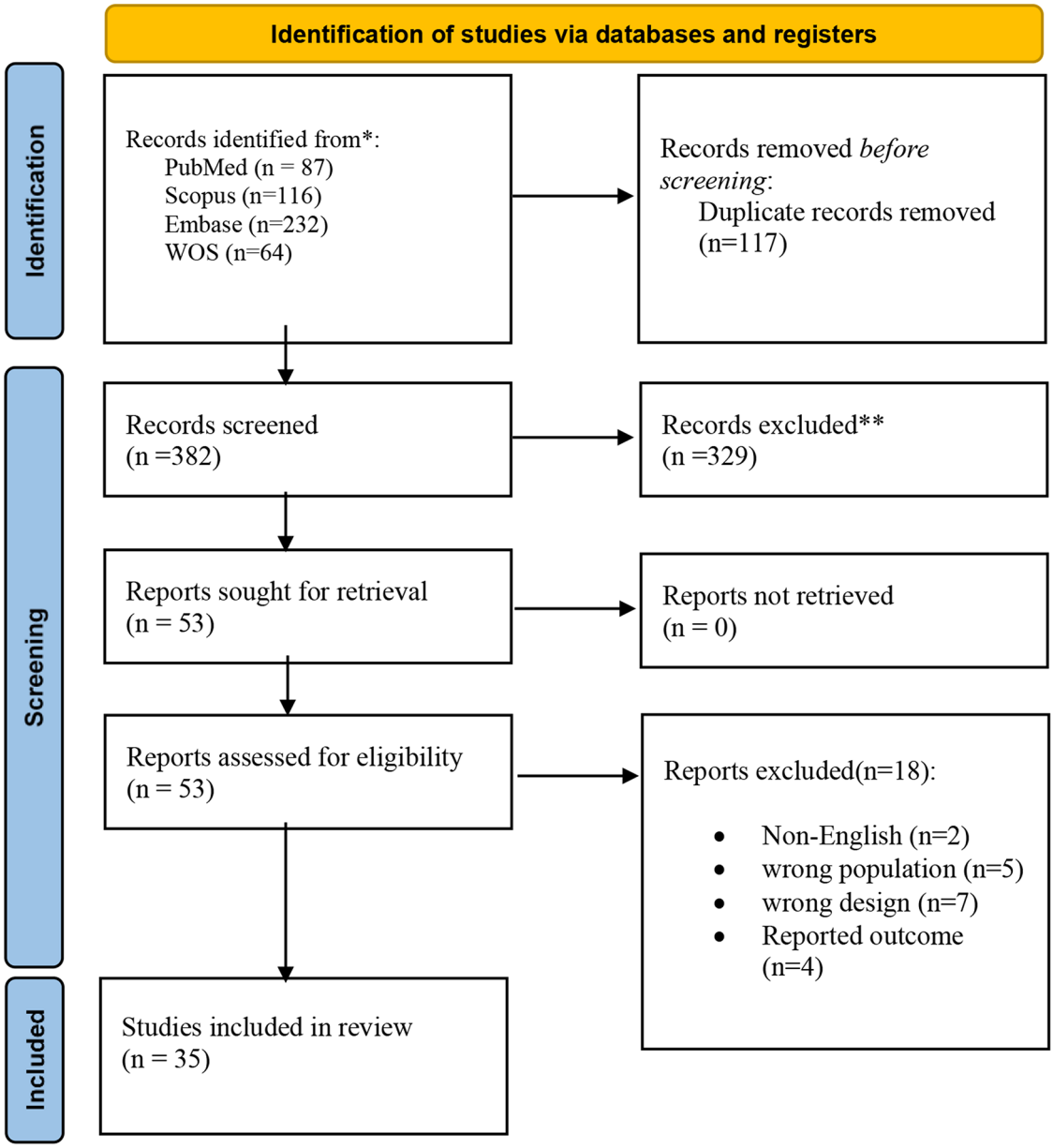

Fig. 1 PRISMA flowchart

SRS characteristics

Different enrolled studies considered distinct modalities and technologies to conduct the treatment process with SRS. The most common technologies were linear accelerator (LINAC), Gamma Knife, CyberKnife, and C-arm LINAC; also, the included studies employed different techniques, such as intensity modulated SRS, volumetric intensity modulated radiosurgery, surface imaging-guided radiosurgery on Trilogy LINAC, Three-dimensional conformal radiotherapy, Volumetric modulated arc radiosurgery, single isocenter for multiple targets dynamic conformal arc, and single-isocenter non-coplanar. The median target volume, reported in 25 studies, ranged from 0.049 to 21.16 cm^3. The median of marginal received dose in patients differed from 7 to 30 Gy (Gy) and mostly went through one fraction of SRS, with some cases of 2 to 5 fractions. SRS isodose line in 22 included studies was reported between 45% and 99%. Regarding radiation-related adverse events, radiation toxicity ($n=56$), local failure ($n=23$), headache ($n=24$), fatigue ($n=15$), seizure ($n=15$), intracranial hemorrhage ($n=8$), cerebral edema ($n=8$), aggravation of pre-existing deficits ($n=4$), nausea ($n=2$), alopecia ($n=2$), encephalitis ($n=1$), and aphasia ($n=1$) were the most frequent adverse events in

Table 1 Demographic characteristics

Author, Year	Country	Type of study	Mean age	Number of Patients	Gender	Study period (Months)
Nath 2009 [20]	USA	Retrospective	53	26	M:10 F:16	38
Kraft 2021 [21]	Switzerland; Germany	Retrospective	61	315	M:177 F:138	61
Mayo 2009 [22]	USA	Prospective	56	12	M:8 F:4	5
Bilger 2017 [23]	Germany and Norway	Retrospective	58	48	M:25 F:23	23
Minniti 2011 [24]	Italy	Prospective	64	102	M:50 F:52	18
Pham 2014 [25]	USA	Retrospective	63	163	M:77 F:86	64
Liepa 2012 [26]	Latvia	Retrospective	59.88	16	M:5 F:11	26
Munshi 2018 [27]	India	Retrospective	51.5	30	N/R	21
De Potter 2012 [28]	Belgium	Retrospective	N/R	38	M:16 F:22	31
Cleary 2017 [29]	USA	Retrospective	58.9	85	M:52 F:33	105
Bossart 2020 [30]	USA	Retrospective	N/R	20	N/R	N/R
Han 2020 [31]	USA	Retrospective	N/R	10	N/R	24
Hanna 2019 [32]	USA	Retrospective	61	32	N/R	84
Minniti 2020 [33]	Italy	Retrospective	60	31	M:15 F:16	11
Vulpe 2019 [34]	USA	Prospective	67	100	M:37 F:63	10
Pan 2012 [35]	USA	Retrospective	61	44	M:19 F:25	21.6
Park 2019 [36]	Korea	Retrospective	55	15	M:7 F:8	24
Breneman 2009 [37]	USA	Retrospective	54	53	M:21 F:32	28
Lohkamp 2018 [38]	Germany	Retrospective	49.5	36	M:27 F:9	5 years
Eder 2022 [39]	Germany	N/R	63	20	M:11 F:9	N/R
Wegner 2021 [40]	USA	Retrospective	61	56	M:22 F:34	19
Furuse 2008 [41]	Japan	Retrospective	62	90	M:47 F:43	89.5
Bennion 2016 [42]	USA	Retrospective	57	109	M:61 F:48	44
Chen 2009 [43]	USA	Prospective	58.9	54	22 M 32 F	0–20 (9)
Kasper 2017 [44]	Israel	Retrospective cohort	61	8	8 F	7 years
Kelly 2010 [45]	USA	Retrospective cohort	61.8	17	9 M 8 F	12.7
Kamath 2005 [46]	USA	clinical	55	64	31 M 33 F	8.2
Roshan 2013 [47]	USA	clinical	57	42	16 M 26 F	13.2
Broemme 2013 [48]	Germany	Retrospective	67	42	23 M 19 F	9.6
Samanci 2021 [49]	Turkey	Retrospective	59.5	58	33 M 25 F	12
Muacevic 2010 [50]	Germany	clinical	60	333	149 M 184 F	7

Table 1 (continued)

Author, Year	Country	Type of study	Mean age	Number of Patients	Gender	Study period (Months)
Giuseppe 2020 [51]	Italy	clinical	57	40	23 M 17 F	10.8
Sameer 2020 [52]	USA	Retrospective	58	65	27 M 38 F	6.2
Steven 2015 [53]	USA	Retrospective	63	15	5 M 10 F	7.1
ST Mok 2017 [54]	Hong-Kong	Retrospective	58	64	40 M 24 F	11.5

M: male, F: female

17 studies, respectively. Table 3 depicts the characteristics of SRS.

Meta-analysis outcomes

The meta-analysis outcomes are divided into survival rates, radiological responses, and complications. Table 4 represents the meta-analysis outcomes.

Survival outcomes

6-months OS rate

Twelve studies reported the 6-month OS rate. The studies demonstrated significant heterogeneity (I2 = 76.45%). Significant variability was verified (Q = 39.69, P-heterogeneity < 0.001), emphasizing the variety of the included research. Furthermore, the 6-month OS rate was 50–89%, and a pooled 6-month OS rate was 75% (95% CI: 68-81%) (Fig. 2).

Meta-regression revealed no significant association between number of brain metastasis (r: −0.0070129, P-value: 0.312), tumor volume (r: −0.0120412, P-value: 0.148), Isodense line (r: −0.3902197, P-value: 0.441), median target volume (r: −0.0020092, P-value: 0.854), prior WBRT (r: 0.1623343, P-value: 0.175), SRS margin dose (r: −0.0061823, P-value: 0.442), and number of SRS fraction (r: −0.0190764, P-value: 0.461).

6-months LC rate

The overall survival rates following therapy in 11 studies were analyzed. There was significant variability among the studies (I^2 = 67.52%). Significant heterogeneity was found between the studies (Q = 35.37, P-heterogeneity < 0.001), highlighting the variety of the included research. Additionally, the 6-month LC rate ranged between 88 and 99%, with a pooled 6-month LC rate of 93% (95% CI: 90-96%) (Fig. 3).

1-year OS rate

Eighteen studies were analyzed to determine the 1-year OS rates. There was significant heterogeneity among the studies (I2 = 93.21%, Q = 486.15, P-heterogeneity < 0.001).). Moreover, Fig. 4 shows that the 1-year OS was between 35 and 95% and a pooled 1-year OS rate of 60% (95% CI: 51-69%).

1-year PFS rate

Three studies reported the 1-year PFS rate, which ranged between 43 and 94%. The results of the study exhibit significant heterogeneity (I2 = 97.66%). The heterogeneity test revealed substantial variations between the studies (Q = 117.00, P-heterogeneity < 0.001). The pooled 1-year PFS rate was 68% (95% CI: 39-98%) (Figure S36).

1-year LC rate

A total of 12 studies reported LC rates over 1-year ranging between 66 and 100%. The analysis indicates significant heterogeneity in the study results (I2 = 93.80%). The heterogeneity test revealed substantial variations amongst the studies (Q = 286.76, P-heterogeneity < 0.001), indicating that the rates that have been reported varied. Figure 5 shows that the pooled 1-year LC rate was 86% (95% CI: 82-90%).

18 months OS rate

We analyzed data from two studies that reported an 18-month OS rate. Significant heterogeneity was seen in the 18-month overall survival rates reported by the various studies (I2 = 93.07%, Q = 14.44, P-heterogeneity < 0.001). The 18-month OS was between 29% and 67%, and a pooled 18-month OS rate of 48% (95% CI: 10-85%) (Figure S37).

2-year OS rate

Five studies reported a 2-year OS rate ranging from 20 to 69%. There is a significant difference in the 2-year OS rates

Table 2 Brain metastasis characteristics

Author, Year	Primary Site	Mean number of Brain metastasis	Total number of brain metastasis	Median tumor volume	Prior treatment	Karnofsky Performance Scale Score (Mean)
Nath 2009 [20]	Breast: 11 Lung: 9 Melanoma: 7	5	138	Maximum target diameter Under 4 cm	WBRT: 6	N/R
Kraft 2021 [21]	NSCLC: 153 Melanoma: 71 Breast: 28 Renal cell: 10 others: 53	3	1087	GTV: 0.2	N/R	KPS score: 90–100:168, 70–80:121, 50–60: 26
Mayo 2009 [22]	Metastatic lung: 7 Melanoma: 1 Metastatic esophagus: 1 Metastatic breast: 1 Metastatic colon: 1 Metastatic renal cell: 1	1.1	14	N/R	Chemotherapy: 2 (Tarceva) WBRT: 7 Conformal Radiation Therapy: 1	N/R
Bilger 2017 [23]	NSCLC: 27 Melanoma: 9 Breast: 7 Others: 5	1.6	77	GTV: 0.4	WBRT: 9	N/R
Minniti 2011 [24]	Lung: 54 Breast: 17 Melanoma: 14 Others: 17	1.5	154	1.6	N/R	KPS > 70
Pham 2014 [25]	Lung: 68 Breast: 25 Melanoma: 24 Renal: 18 GI: 8 Gynecological cancer: 5 Head & neck: 2 Other: 13	1	490	N/R	surgical resection: 43 WBRT: 4	N/R
Liepa 2012 [26]	Breast: 8 Melanoma: 2 Lung: 3 Ovary & cervix: 2 non-Hodkin's lymphoma: 1	1.6	27	N/R	8 patients received WBRT (3 Gy in 10 fractions to a total dose of 30 Gy)	KPS > 70
Munshi 2018 [27]	Lung: 3 and the rest were original brain tumors.	N/R	N/R	N/R	N/R	N/R
De Potter 2012 [28]	Lung: 19 Breast: 9 Colon: 2 Skin: 2 Other: 6	1.5	58	GTV: 12.9	N/R	70 < KPS < 80
Cleary 2017 [29]	Breast: 8 Colorectal: 3 Head and neck: 1 Melanoma: 18 NSCLC: 34 Renal cell: 9 SCLC: 2 Other: 10	3.8	325	9.8	WBRT: 4	N/R
Bossart 2020 [30]	10p: benign skull base tumors 10p: have metastases	N/R	All lesion: 27 metastatic lesion: 17 benign skull base tumors: 10	N/R	N/R	N/R
Han 2020 [31]	N/R	2.2	22	N/R	N/R	N/R

Table 2 (continued)

Author, Year	Primary Site	Mean number of Brain metastasis	Total number of brain metastasis	Median tumor volume	Prior treatment	Karnofsky Performance Scale Score (Mean)
Hanna 2019 [32]	N/R	4	141	15.9	N/R	N/R
Minniti 2020 [33]	Lung: 14 Breast: 5 Melanoma: 8 Ovary: 1 Kidney: 3	N/R	204	3.9 ± 1.93 cm3	N/R	0.07, 0.09
Vulpe 2019 [34]	Lung: 18 Breast: 5 Melanoma: 3 Other: 16	N/R	96	N/R	WBRT: 2/42	N/R
Pan 2012 [35]	Lung: 18 Breast: 8 Melanoma: 7 GI: 5 Renal: 3 Others: 3	20	115	N/R	WBRT: 6/44 Surgery: 5/44	N/R
Park 2019 [36]	NSCLC: 8 Breast carcinoma: 2 Melanoma: 2 Adenocarcinoma: 1 Renal cell carcinoma: 1 Hepatocellular carcinoma: 1	N/R	17	19.53 ± 7.07	Radiosurgery: 4 Surgical resection and WBRT: 2 Surgical resection and radiosurgery: 1 WBRT: 1 Surgical resection: 1	90
Breneman 2009 [37]	Lung: 28 Melanoma: 11 Breast: 9 Other: 5	2	158	0.2	WBRT: 32	N/R
Lohkamp 2018 [38]	Breast carcinoma: 17 Bronchial carcinoma: 11 Colorectal cancer: 2 Malignant melanoma: 2 Others: 4	5	140	1.26	WBRT: all chemotherapy: 33/36	70
Eder 2022 [39]	N/R	3	75	0.11	N/R	N/R
Wegner 2021 [40]	Lung (NSCLC/SCLC/LCNEC): 32 Breast: 12 Melanoma: 7 GI: 3 Others: 2	N/R	154	N/R	WBRT: 10/56 surgery: 4/56	60: 2p 70: 6p 80: 31p 90: 16p 100: 1p
Furuse 2008 [41]	Lung cancer: 55 Breast cancer: 15 Rectal, colon cancer: 6 Renal cell carcinoma: 3 Gastric cancer: 1 Others: 10	N/R	N/R	N/R	WBRT: 4/90	N/R
Bennion 2016 [42]	Squamous cell carcinoma: 6 Adenocarcinoma: 42 Renal cell: 11 Melanoma: 25 Others: 25	2	170	0.89	WBRT: 57/109	80

Table 2 (continued)

Author, Year	Primary Site	Mean number of Brain metastasis	Total number of brain metastasis	Median tumor volume	Prior treatment	Karnofsky Performance Scale Score (Mean)
Chen 2009 [43]	Breast: 17 Choriocarcinoma: 1 Colon: 1 Esophageal: 2 Lung, NSCLC: 19 Lung, SCLC: 3 Melanoma: 6 Renal: 2 Gastric: 2 Unknown primary: 1	4 or fewer	108	0.98 cm3	WBRT: 46/54	70 or greater
Kasper 2017 [44]	Endometrial cancer: 1 Ovarian Cancer: 7	2.5	20	N/R	systemic therapy: 8/8 WBRT: 1/8 surgical resection: 3/8	70
Kelly 2010 [45]	NSCLC: 6 Melanoma: 6 Others: 5	1	Frontal: 1 Temporal: 2 Parietal: 6 Occipital: 7 Cerebellum: 2 Total: 18	N/R	WBRT: 1/17	80
Kamath 2005 [46]	NSCLC: 26 SCLC: 6 Renal: 6 Breast: 6 Ovary/fallopian: 4 Melanoma: 4 Colon: 4 Esophagus: 1 Prostate: 1 Unknown primary: 3	2	35	N/R	WBRT: 20/64 surgical resection: 16/64 surgical resection + WBRT: 11/64	N/R
Roshan 2013 [47]	Lung: 12 Breast: 11 Melanoma: 10 Kidney: 3 Other: 3 Colorectal: 2 Ovarian: 1	2	94	0.3 cc	WBRT: 11/42 SRS: 19/42	≥ 70
Broemme 2013 [48]	NSCLC: 19 Melanoma: 9 GI cancer: 6 Breast cancer: 5 Gynecological cancer: 2 cancer of unknown primary origin: 1	N/R	23	N/R	Radiosurgery: 1/42 WBRT: 15/42	80
Samanci 2021 [49]	Lung (NSCLC): 24 Breast: 12 Colorectal: 8 Genitourinary (Kidney Bladder Prostate): 7 Malign melanoma: 4 Salivary gland: 3	2	76	1.3 cm3	Cytotoxic therapy: 19 Hormone therapy: 14 Targeted therapy: 2 Surgical resection: 20 Radiosurgery: 1 WBRT: 9	90

Table 2 (continued)

Author, Year	Primary Site	Mean number of Brain metastasis	Total number of brain metastasis	Median tumor volume	Prior treatment	Karnofsky Performance Scale Score (Mean)
Muacevic 2010 [50]	NSCLC: 80 SCLC: 19 GUT: 53 GI: 47 Melanoma: 37 Breast: 85 Others: 12	N/R	783	1 cc	Chemotherapy: 200/333 WBRT: 72/333	90
Giuseppe 2020 [51]	Lung: 17 Breast: 7 Melanoma: 10 Kidney: 6	13	527	0.38	Immunotherapy: 12/40 Targeted agents: 6/40	≥60
Sameer 2020 [52]	Lung: 28 Breast: 20 Melanoma: 12 Ovarian: 2 Other: 3	2	204	N/R	N/R	N/R
Steven 2015 [53]	Lung: 5 Breast: 4 Melanoma: 5 Others: 1	3	62	size: 18 mm	N/R	N/R
ST Mok 2017 [54]	Breast: 7 Lung: 45 GI: 2 Renal cell: 6 Thyroid: 1 Osteosarcoma: 1 Germ cell: 1 Epithelioid Hemangioendothelioma: 1	N/R	94	N/R	WBRT: 10	80

Abbreviations N/R: not reported, NSCLC: non-small cell lung cancer, LCNEC: large cell neuroendocrine carcinoma, SCLC: small cell lung cancer, GI: gastrointestinal, GTV: gross tumor volume, KPS: Karnofsky Performance Scale, WBRT: whole brain radiotherapy, SRS: stereotactic radiosurgery

(I2 = 92.38%, Q = 48.09, P-heterogeneity < 0.001) between studies. The pooled 2-year OS rate was 39% (95% CI: 19-58%) (Figure S38).

2-year PFS rate

Three studies reported 2-year PFS rates, and significant heterogeneity among the studies was evident (I2 = 92.34%, Q = 24.99, P-heterogeneity < 0.001). The rate of 2-year PFS ranged from 59 to 88%, and the pooled 2-year PFS rate was 75% [95% CI: 58-91%] (Figure S39).

Radiological outcomes

The radiological outcomes, including complete response rate, partial response rate, progressive disease rate, and stable disease rate, were reported separately (Fig. 6).

Complete response rate

Seven studies reported a complete response rate ranging from 11–37%with a pooled rate of 26% [95%CI:20-33%]. Moreover, significant heterogeneity was determined between studies (I2:82.24%, P-heterogeneity < 0.001, Q:34.05 (Fig. 6).

Partial response rate

Seven studies determined that the partial response rate varied between 15% and 71%. The pooled rate of partial response rate was 38% [95%CI:24-51%]. The heterogeneity among the studies was remarkably determined by I2:95.59%, Q:132.91, and P-heterogeneity < 0.001 (Fig. 6).

Stable disease rate

The stable disease rate was reported in seven studies. The stable disease rate varied between 5 and 48% with a pooled rate of 29% [95%CI:17-41%]. The heterogeneity was high

Table 3 SRS characteristics

Author, Year	Modality of SRS	Interval between Tumor Diagnosis and SRS	Median target volume (in cm3)	SRS margin dose (mean or median in Gy)	SRS Isodose line (%)	Number of SRS fractions	Adverse radiation effects rate
Nath 2009 [20]	LINAC IM-SRS	N/R	N/R	Median: 18 Gy	90	1	N/R
Kraft 2021 [21]	LINAC	N/R	N/R	18	80	12p: 1 4p: 3–5	N/R
Mayo 2009 [22]	volumetric IMRT	N/R	CTV: 1.20 ± 1.69 PTV: 2.35 ± 6.01	1p: 15 11p: 7	96	26p: 1 4p: 2–5	N/R
Bilger 2017 [23]	LINAC	N/R	N/R	2p: 18 75p: 20	80	5	N/R
Minniti 2011 [24]	LINAC	N/R	Treated volume: 2.2	86p: 20 44p: 18 24p: 16	80–90	5	N/R
Pham 2014 [25]	SIG-RS on Trilogy LINAC	N/R	N/R	22	N/R	1	N/R
Liepa 2012 [26]	IGRS	N/R	18.63	12p: 18 4p: 15.35	80	8p: 3 2p: 5	N/R
Munshi 2018 [27]	Three-dimensional conformal radiotherapy VMAT	N/R	PTV: 6.0 cm3	14	N/R	N/R	N/R
De Potter 2012 [28]	WBRT plus HSRT	N/R	PTV: 8.6	30	N/R	1	N/R
Cleary 2017 [29]	Novalis TxTM linear accelerator-based	N/R	9.8	30	N/R	1 fraction: 20 3 fractions: 24 5 fractions: 25	N/R
Bossart 2020 [30]	Gamma Knife	N/R	N/R	12	N/R	1 fraction: 41 5 fraction: 3	N/R
Han 2020 [31]	LINAC	N/R	PTV: 18.31	27.0	LINAC plans: 97.7 Gamma Knife plans: 98.5 CyberKnife plans: 98.4	3 fractions	N/R
Hanna 2019 [32]	SRS with VMAT	N/R	N/R	17, 18, 20	Gamma Knife plans: 98.5	1 fraction	N/R
Minniti 2020 [33]	SIMT DCA	N/R	0.89	71p: 22 115p: 20 18p: 16–18	CyberKnife plans: 98.4	1 fraction	local failure: 4p
Vulpe 2019 [34]	Gamma Knife	N/R	1.919	1 fraction: 20 3 fractions: 24 5 fractions: 25	N/R	1 (single-fraction)	Fatigue: 8p nausea: 1p headache: 4p Seizure: 3p muscles weakness:3 p cerebral edema: 1p intracranial hemorrhage: 1p encephalitis: 1p local failure: 16p percent: 39%

Table 3 (continued)

Author, Year	Modality of SRS	Interval between Tumor Diagnosis and SRS	Median target volume (in cm3)	SRS margin dose (mean or median in Gy)	SRS Isodose line (%)	Number of SRS fractions	Adverse radiation effects rate
Pan 2012 [35]	SIG-RS LINAC	N/R	N/R	20	99	1 (single-fraction)	fatigue and dizziness: 2/8 headache: 3/8 headache, nausea, and vomiting after seizure: 1/8 hemorrhage and seizure after treatment: 1/8 aphasia: 1/8
Park 2019 [36]	Gamma Knife	N/R	21.16	7 Gy×3fraction: 3 8 Gy×3fraction: 5 9 Gy×3fraction: 2 10 Gy×3fraction: 5 8 Gy×5fraction: 2	N/R	single-fraction	died: 1p
Breneman 2009 [37]	LINAC	N/R	N/R	1 fraction: 18	50 (50–70)	NR	9.60%
Lohkamp 2018 [38]	CyberKnife	3.6 Year	0.46	18	N/R	1 (single-fraction)	Aggravation of pre-existing deficits: 4 Radiation toxicity: 8 Fatigue: 2 General deterioration (KPS): 1 Alopecia: 2 total: 22.8%
Eder 2022 [39]	single-isocenter non-coplanar	N/R	0.28	19	50	1 (single-fraction)	N/R
Wegner 2021 [40]	Gamma Knife	N/R	0.049	20	N/R	1 (single-fraction)	local failure: 3/56
Furuse 2008 [41]	C-arm LINAC	N/R	N/R	20	70	1 (single-fraction)	N/R
Bennion 2016 [42]	Gamma Knife	N/R	1.89	18	98	1: 72/94 3-5: 22/94	Symptomatic necrosis: 6 lesions (6%)
Chen 2009 [43]	LINAC	108 days	≥ 1 cm3 and < 1 cm3	18	50	4: 5P 6: 6P 10: 10P	No
Kasper 2017 [44]	Cyberknife™	N/R	2	16–25	N/R	3 and 5 (median = 3)	No
Kelly 2010 [45]	LINAC	long interval	3.49	18	N/R	1 (single-fraction)	11.10%
Kamath 2005 [46]	LINAC	N/R	N/R	17.5	80	1: 282/333 2: 43/333 3: 8/333	No
Roshan 2013 [47]	DCA: 70 /94 IMRS: 24/94	N/R	0.8	Median marginal dose: 21 Median maximum dose: 25.1	95	1	9.50%
Broemme 2013 [48]	LINAC	40d	11.1	17	99	1	2.38%
Samanci 2021 [49]	Gamma Knife	2.5w	6.15	27	70 or 80	1	headache, dizziness, and somnolence; 19% headache: 3.5% edema cerebra: 5.2% total: 27.7%

Table 3 (continued)

Author, Year	Modality of SRS	Interval between Tumor Diagnosis and SRS	Median target volume (in cm3)	SRS margin dose (mean or median in Gy)	SRS Isodose line (%)	Number of SRS fractions	Adverse radiation effects rate
Muacevic 2010 [50]	CyberKnife	N/R	1	18.5	80	1	Hemorrhage: 4/333 Radiation toxicity: 48/333 15.6%
Giuseppe 2020 [51]	LINAC	N/R	7.3	22: 417/527 20: 57/527 16–18: 53/527	N/R	12p: 1 4p: 3–5	Intracranial hemorrhage: 2/40 seizure: 1/40 and headache: 2/40 total: 12.5%
Sameer 2020 [52]	CyberKnife linac	N/R	N/R	18	45	26p: 1 4p: 2–5	5%
Steven 2015 [53]	VMAT	N/R	1.5	20	70	5	seizure: 1/15 total: 6.7%
ST Mok 2017 [54]	LINAC	N/R	1.5	18	98	5	Acute toxicities and brain oedema: 4 seizure: 9 total: 18.8%

Abbreviations N/R: not reported, LINAC: linear accelerator, IM-SRS: intensity modulated stereotactic radiosurgery, IMRT: intensity modulated radiotherapy, SIG-RS: surface imaging guided radiosurgery, WBRT: whole brain radiotherapy, HSRT: hypo fractionated stereotactic radiotherapy, VMAT: Volumetric modulated arc therapy, SIMT DCA: single isocenter for multiple targets dynamic conformal arc. CTV: clinical target volume, PTV: planning target volume, Gy: gray

Table 4 Meta-analysis outcomes

Outcomes	Minimum rate	Maximum rate	Pooled Rate	95%CI	I^2 metrics	Q value	Chi-square *P*-value
Survival Rate							
• 6-month OS	50%	89%	75%	68-81%	76.45%	39.69	< 0.001
• 1-Year OS	35%	95%	60%	51-69%	93.21%	486.15	< 0.001
• 18-month OS	29%	67%	48%	10-85%	93.07%	14.44	< 0.001
• 2-year OS	20%	69%	39%	19-58%	92.38%	48.09	< 0.001
• 6-month LC	88%	99%	93%	90-96%	67.52%	35.37	< 0.001
• 1-year LC	66%	100%	86%	82-90%	93.80%	286.76	< 0.001
• 1-year PFS	43%	94%	68%	39-98%	97.66%	117.00	< 0.001
• 2-year PFS	59%	88%	75%	58-91%	92.34%	24.99	< 0.001
Radiological Response							
• Complete response	11%	37%	26%	20-33%	82.24%	34.05	< 0.001
• Partial response	15%	71%	38%	24-51%	95.59%	132.91	< 0.001
• Progressive disease	3%	47%	12%	2-22%	97.70%	88.20	< 0.001
• Stable disease	5%	48%	29%	17-41%	94.91%	118.03	< 0.001
Adverse Radiation Effect							
• Symptomatic	1%	27%	8%	3-13%	91.58%	37.76	< 0.001
• Asymptomatic	2%	14%	9%	1-16%	83.03%	12.36	< 0.001
Radionecrosis							
• Grade 2	4%	14%	8%	-2-18%	78%	4.55	0.03
• Grade 3	1%	5%	3%	0–5%	2.4%	1.47	0.48
• > Grade 2	1%	7%	4%	0–8%	49.71%	3.94	0.14
• > Grade 1	1%	28%	14%	-1-29%	92.46%	28.40	< 0.001
• Grade 1 or 2	1%	27%	15%	3-27%	88.88%	34.67	< 0.001
• Grade 2 or 3	1%	17%	9%	2-17%	80.72%	19.08	< 0.001
• Total	2%	28%	9%	4-14%	88.03%	59.09	< 0.001

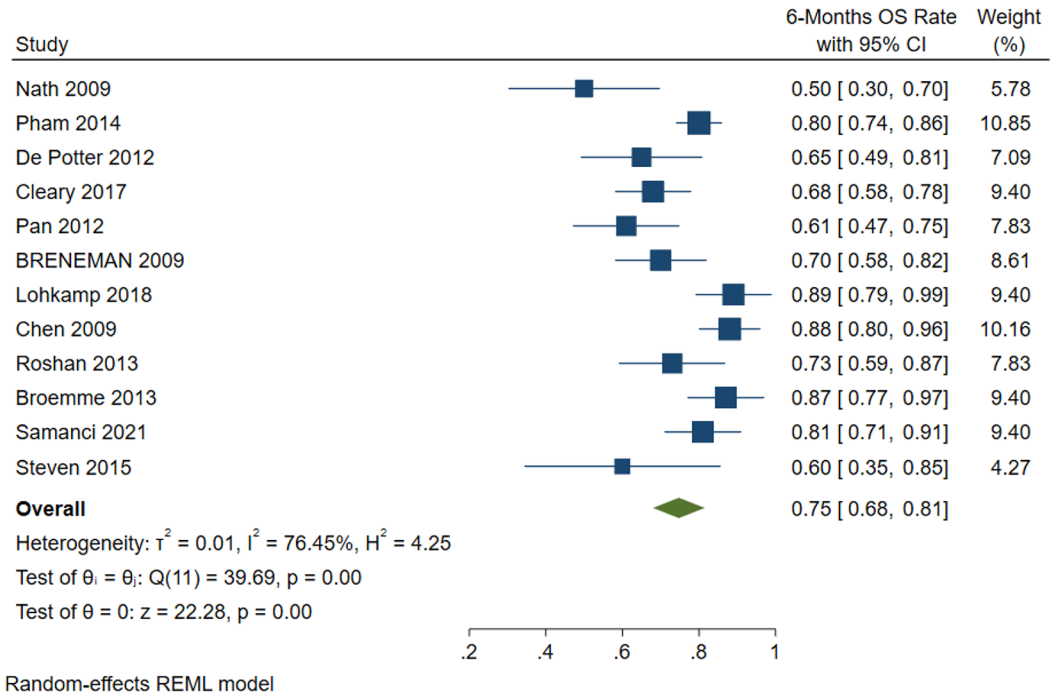

Fig. 2 The forest plot of pooled 6-months OS rate

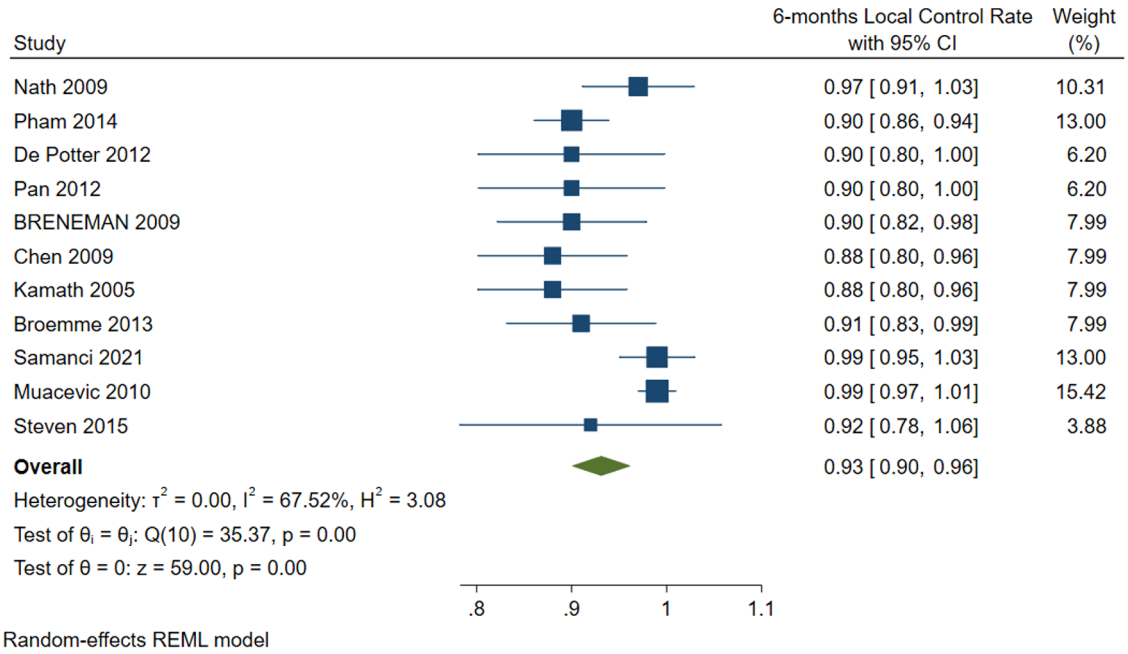

Fig. 3 The forest plot of pooled 6-months LC rate

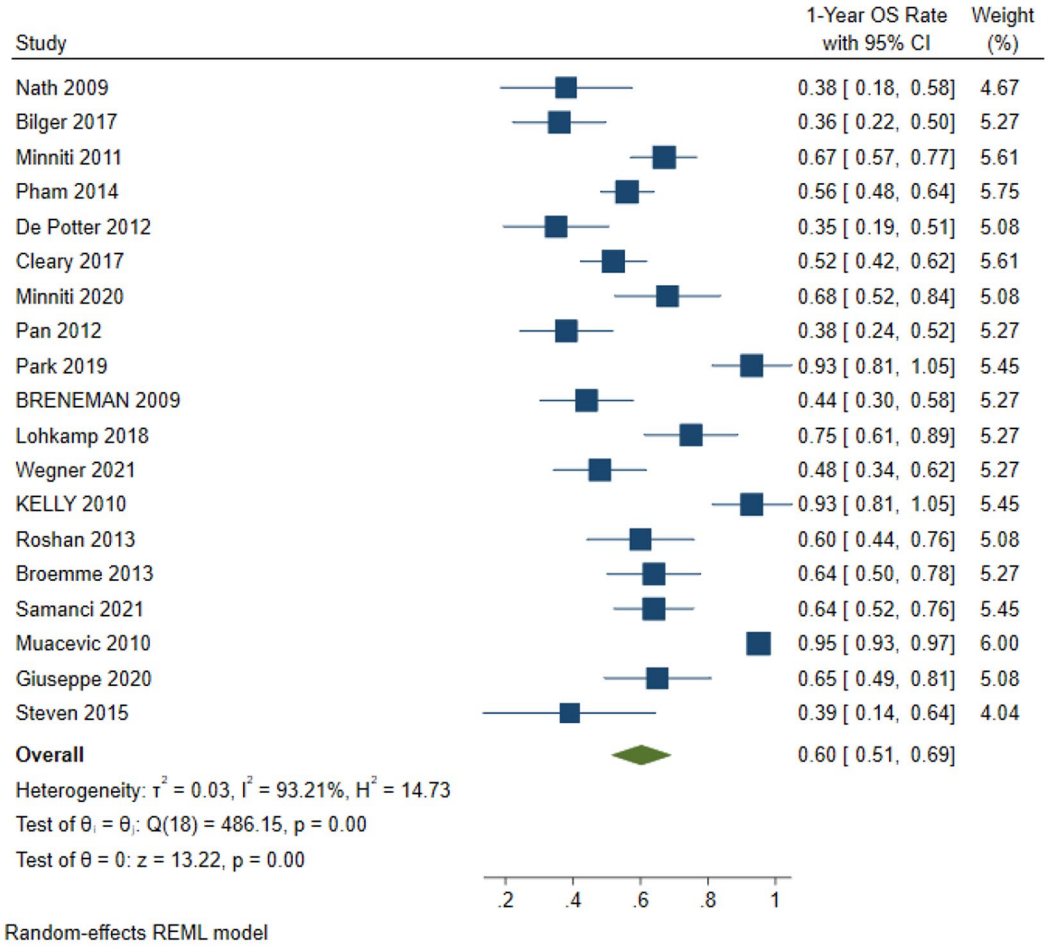

Fig. 4 The forest plot of pooled 1-year OS rate

between the studies, with an I2:94.91%, Q:118.03, and P-heterogeneity < 0.001 (Fig. 6).

Progressive disease rate

Eight studies reported progressive disease rates ranging from 3 to 47%. The pooled rate of progressive disease was 12% [95%CI:2-22%]. I2:97.70%, Q:88.20, and P-heterogeneity48 determined significant overall heterogeneity (Fig. 6).

Adverse radiation effect

The results from nine studies indicated symptomatic adverse radiation effects ranging between 0.01 and 0.27, with a pooled rate of 8% [95%CI:3-13%]. Adverse asymptomatic radiation effects were found in three studies, ranging between 2% and 14%, with a pooled rate of 9% [95%CI:1-16%]. Interestingly, a test of group difference revealed no significant difference between the pooled rate of symptomatic and asymptomatic adverse radiation effect (P-value:0.82) (Figure S40).

Radionecrosis

One significant side effect of radiotherapy is radiation necrosis. According to several studies, the pooled rate of grade 2 radiation necrosis was found to be 8% [95%CI: -2-18%], while the rate of grade 3 radiation necrosis was reported in three studies with a pooled rate of 3% [95%CI:0-5%]. Additionally, three studies reported grade > 1 radiation necrosis with a pooled rate of 14% [95%CI: -1-29%]. The pooled grade > 2 radiation necrosis rate was determined in three studies, and the result was 4% [95%CI:0-8%]. The pooled rate of radiation necrosis in grades 1 or 2 and 2 or 3 was found to be 15% [95%CI:3-27%] and 9% [95%CI: 2-17%], respectively. Overall, regardless of grade, the total pooled rate of radiation necrosis was 9% [95%CI: 4-14%] (Figure S41).

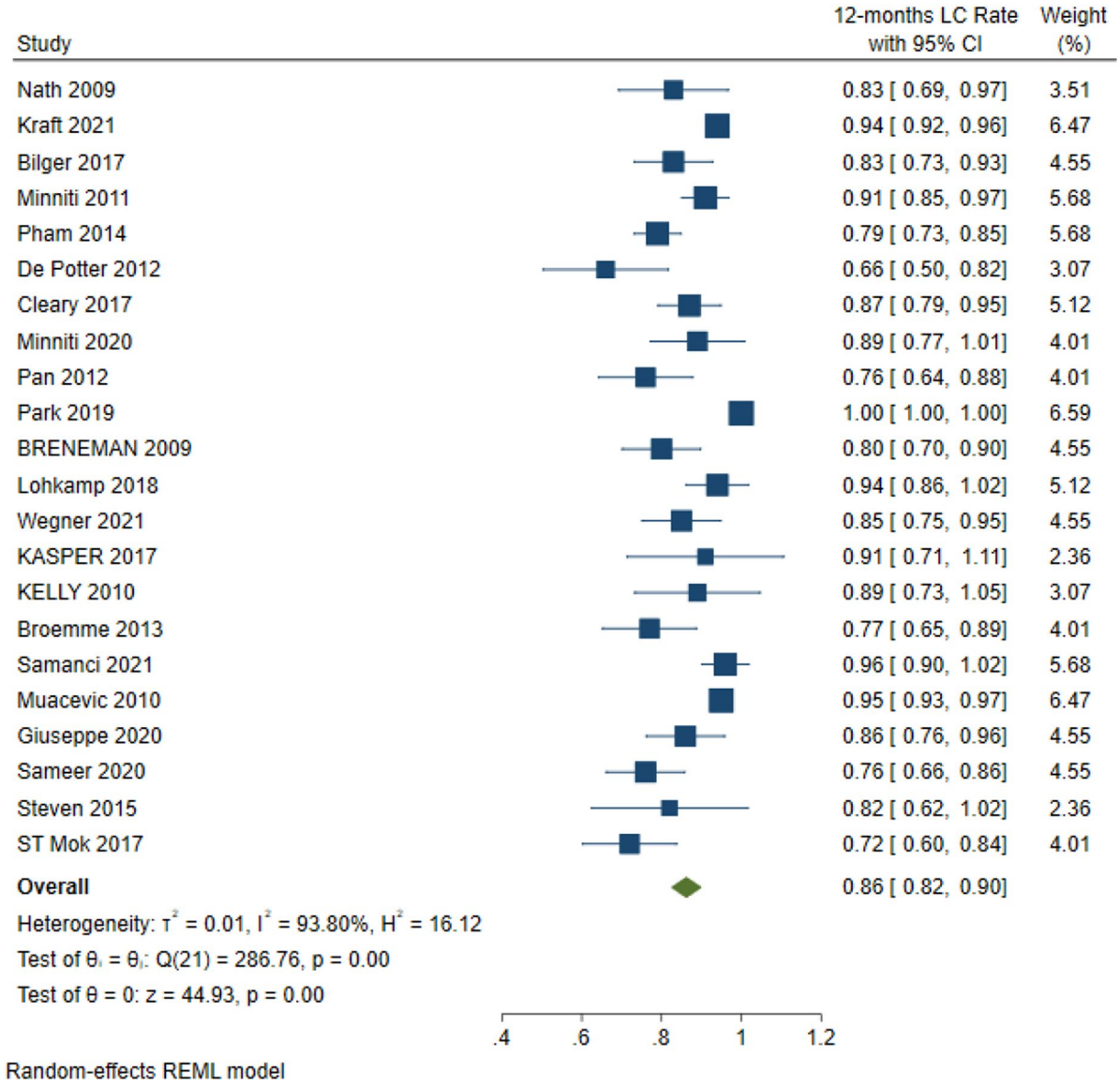

Fig. 5 The forest plot of pooled 12 months LC rate

Further therapy

Fourteen studies have reported the need for further treatment using WBRT ranging from 0.06 to 0.36 and a combined rate of 16% [95%CI:12-21%]. Nine studies included surgery as a further treatment, with rates ranging from 0.02 to 0.48 and a combined rate of 6% [95%CI: 0-12%]. Salvage SRS was necessary according to 12 studies, with rates varying from 2 to 50% and a combined rate of 15% [95%CI:7-22%]. Further therapies beyond SRS, surgery, and WBRT were reported in two studies, with rates ranging from 5 to 13%. The combined rate of such treatments was 5% [95%CI:0-11%]. However, four studies reported no need for further treatment, with rates ranging from 2 to 7% and a combined rate of 3% [95%CI:0-7%].

Sensitivity analysis

A sensitivity analysis was performed for each of the pooled estimates to assess the robustness of our outcomes; thus, we went over the analysis many times, with one excluded study each time. As a result of excluding each study, the rerun analysis indicated robust results for 6-months OS (p-value < 0.05 for each study), 6-months LC (p-value < 0.05 for each study), 1-year OS (p-value < 0.05 for each study), 1-year PFS (p-value < 0.05 for each study), 1-year LC (p-value < 0.05 for each study), 18 months OS

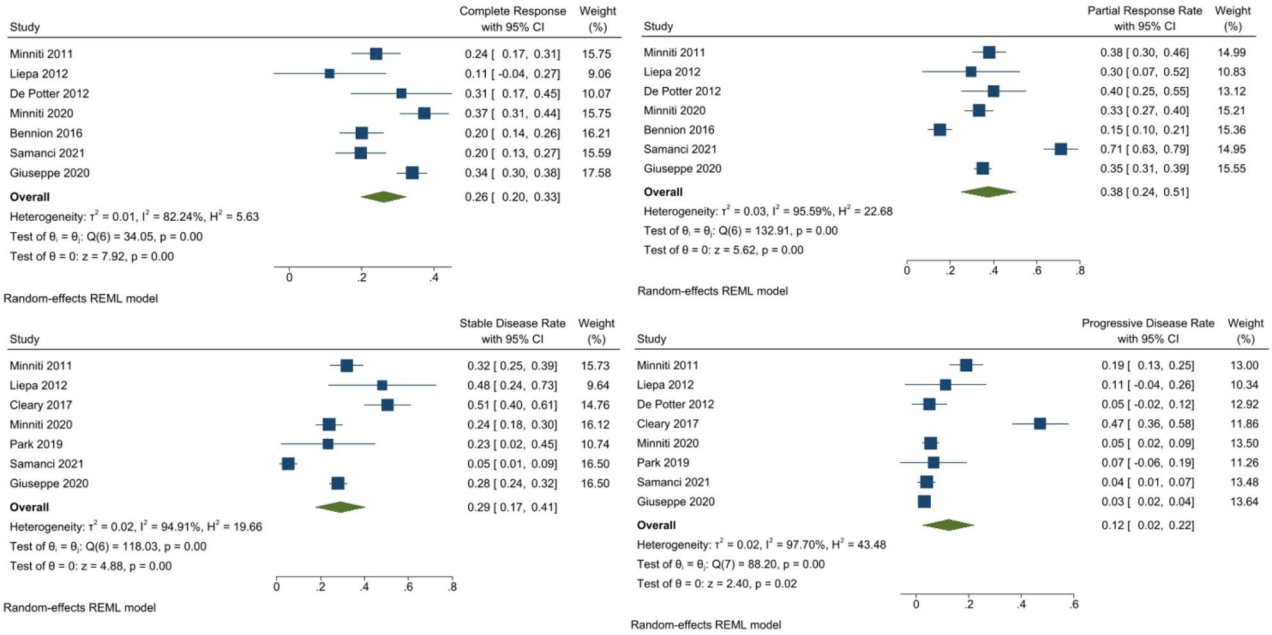

Fig. 6 The forest plots of radiological response rates

(p-value < 0.05 for each study), 2-year OS (p-value < 0.05 for each study), 2-year PFS (p-value < 0.05 for each study), complete response rate (p-value < 0.05 for each study), stable disease rate (p-value < 0.05 for each study), and partial response rate (p-value < 0.05 for each study). However, no robust outcome was determined for the progressive disease rate.

Publication bias

Egger's regression asymmetry test was conducted to evaluate the publication bias that suggested no significant publication bias concerning complete response rate ($p = 0.3656$), partial response rate ($p = 0.9929$), stable disease rate ($p = 0.2728$), progressive disease rate ($p = 0.3084$), 2-Year OS rate ($p = 0.12$), 1-Year PFS rate ($p = 0.42$), and 2-Year PFS rate ($p = 0.12$); however, there was significant bias regarding 6-Months OS rate ($p = 0.00$), 1-Year OS rate ($p = 0.01$), 6-months LC rate ($p = 0.04$), and 12-months LC rate ($p = 0.00$). In the cases of considerable publication bias, the trim and fill method was employed to achieve more symmetrical funnel plots and determine the influence of missing studies on estimated effect sizes. Using the trim and fill method, we generated an updated pooled estimate for 6-Months OS rate, 1-Year OS rate, and 6-month LC rate, which were 78% (95% CI: 75-81%), 84% (95% CI: 82-86%), and 96% (95% CI: 94-97%), respectively.

Discussion

SRS, with or without WBRT, should be considered as the first-line therapeutic option for BM [55]. Compared to the typical frame-based SRS, non-invasive, frameless SRS improves patient comfort and minimizes anxiety. Frameless SRS also simplifies providing fractionated radiation, which may be effective when BMs are big, irregularly shaped, or located near essential tissues [56–60]. Kondziolka et al. observed a 9% discomfort rate during frame installation despite utilizing sedatives [61]. Furthermore, using SRS without WBRT resulted in fewer adverse effects, such as cognitive impairment [62]. Andrews et al. [9] reported no differences in outcomes between Gamma Knife and LINACs for BMs, whether SRS was used with or without WBRT. The effectiveness of frameless-based SRS for extracranial malignancies has been extensively demonstrated [63].Based on the findings of this meta-analysis, it is evident that frameless radiosurgery leads to improved OS, PFS, and LC rates in patients with BMs. Our study has determined the pooled estimated survival rates at six months, one year, 18 months, and two years for OS and PFS, as well as the six-month and 12-month LC rates. The results demonstrate that a significant proportion of patients experienced improved survival following frameless radiosurgery, with a pooled 6-month OS rate of 75% and a 1-year OS rate of 60%. Moreover, evidence suggests that frameless radiosurgery may offer long-term survival benefits, with estimated OS rates of 48% at 18 months and 39% at two years. Additionally, the PFS rate estimates indicate positive outcomes, with estimated

1-year and 2-year PFS rates of 68% and 75%, respectively, signifying that a substantial number of patients were able to avoid disease progression. Notably, the pooled 6-month and 12-month LC rate estimates showed significant improvement at 93% and 86%, respectively, highlighting the effectiveness of frameless radiosurgery in controlling local tumors.The feasibility and toxicity of CyberKnife Frameless SRS (CK-SRS) were examined in a study. The remaining five patients had a median follow-up length of 19 months. The entire cohort had a median survival duration of 12 months after CK-SRS. The two-year rates for LC, CSS, and OS were 26%, 26%, and 22%, respectively. Symptoms improved or remained stable following CK-SRS, except for one patient who reported greater pain. The treatment was well tolerated, with just one case of Grade 2 and 3 mucositis [64].An analysis of LINAC-based frameless SRS techniques for BM patients was conducted by Ibrahim et al. [65]. Overall, the median survival and time were 8.7 and 5.3 months, respectively. LR as a first event was 25% and 38% after one and two years, respectively, while distant brain recurrence as a first event was 18% and 21%. 31% of patients died before experiencing a brain event. A study examined the outcome and prognostic characteristics of LINAC-based frameless SRS in BM from malignant melanoma. The median follow-up period was seven months, while the median OS was nine months. The 6-, 12-, and 24-month OS rates were 71%, 39%, and 25%, respectively. The median intracerebral control period was 5.3 months, with 6- and 12-month intracerebral PFS rates of 48% and 38%, respectively. The most prevalent clinical adverse effect was headache. The most prevalent radiological result during follow-up was localized edema in the SRS high-dose location [66].Lee et al. [67] studied the effectiveness of VMAT in sequential or simultaneous integrated tumor boost in WBRT for patients with poor prognosis and four or more BMs. The follow-up period spanned 0.3 to 16.5 months. The OS at six and twelve months was 66.7% and 41.7%, respectively. The local PFS at six and twelve months was 100% and 62.5%. In research by Nichol et al. [68], 60 patients with one to 10 BMs who received fractionated therapies were evaluated. At 30.5 months of follow-up, the median survival was 10.1 months, the rates of complete and partial brain response rates were 56%, and LC was 88%. Zhexi et al. [69] investigated the outcomes of frame-based and frameless LINAC SRS. The average follow-up time was 13.2-year s. The total obliteration rate was similar (Frame-based 82.5% vs. Frameless 80.0%) and did not change significantly over time (log-rank $p = 0.536$). Both frameless and frame-based LINAC SRS are equally successful in obliterating intracranial arteriovenous malformations. In research by Lau et al., single-isocenter frameless VMAT was administered in 15 patients, with a median dosage of 20 Gy in three BMs. The median follow-up period was 7.1 months. At one year, local and regional control was obtained in 81.5% and 60% of cases, respectively, with an OS of 39%; there was no treatment-related toxicity of grade 3 or above. There was no evident link between the dosage administered to normal brain tissue and the level of toxicity [70].An experiment examined LC, brain-distant progression (BDP), toxicity, and OS in BM patients treated with hypofractionated stereotactic radiotherapy (HSRT). In 1.2 years after therapy, the median LC rate was 30 months (96.96%), the median BDP rate was 24 months (12.24%), and the median OS rate was 14 months (69.33%). KPS and managed extracranial disease were linked with a considerable survival advantage [71]. In a study of 98 patients with BMs, Kim et al. discovered that HSRT patients had equal LC and OS rates and a decreased risk of toxicity compared to those treated with SRS. This was even though HSRT was utilized on big lesions in difficult places [72].Buss et al. [73] evaluated the LC of BM treated with single-fraction SRS using frameless or frame-based immobilization. The median follow-up duration for frameless SRS was 10.5 months, while framed SRS took 7 months. Patients treated with frameless SRS had greater neurological symptoms before treatment and were more likely to get a tyrosine kinase inhibitor concurrently or within 4 weeks of treatment. The frameless SRS group exhibited a larger average metastatic volume than the frame-based SRS group, although the difference was insignificant. At one year, LC in BM treated with frameless SRS was 92%, compared to 86% for framed SRS. OS was comparable between groups ($p = 0.46$).

Limitations

It is important to note that there is considerable heterogeneity across the studies we have analyzed. Differences in patient demographics, treatment methods, and outcome measures can all contribute to this variability, impacting our findings' overall reliability and generalizability. Despite employing a random-effects model to address heterogeneity, residual variability among studies may still impact the strength of our conclusions. Additionally, the potential for publication bias is a significant limitation. Despite our use of sensitivity analysis and the trim and fill technique to mitigate publication bias, excluding unpublished or negative studies could introduce bias into our pooled estimates, potentially compromising the integrity and dependability of our findings. Furthermore, variations in the quality and methodology of the included studies may influence the overall reliability of our findings and impact their internal validity.

Conclusion

The meta-analysis presents compelling evidence supporting the effectiveness of frameless radiosurgery in improving the 6-month, 1-year, and 2-year overall survival rates, as well as progression-free survival and local control rates in patients with brain metastases. These results indicate that frameless stereotactic radiosurgery has a positive impact on both survival and local disease control. However, due to significant variability among the studies, it is essential for future research to focus on standardizing treatment protocols and outcome measures to draw more definitive conclusions. Furthermore, our study highlights the importance of conducting prospective trials to confirm these findings and potentially influence clinical guidelines. Despite some limitations, such as publication bias and study variations, this meta-analysis provides a foundation for a potential shift in treatment approaches. It underscores the need to integrate advanced radiosurgical techniques in the management of brain metastases, which could lead to improved patient outcomes and should be considered in clinical practice.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval The study is deemed exempt from receiving ethical approval.

Consent to participate Not applicable.

Consent for publication Not applicable.

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