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A Bayesian network meta-analysis of whole brain radiotherapy and stereotactic radiotherapy for brain metastasis

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Abstract

This study was conducted to compare the effects of whole brain radiotherapy (WBRT) and stereotactic radiotherapy (SRS) in treatment of brain metastasis.

A systematical retrieval in PubMed and Embase databases was performed for relative literatures on the effects of WBRT and SRS in treatment of brain metastasis. A Bayesian network meta-analysis was performed by using the ADDIS software. The effect sizes included odds ratio (OR) and 95% confidence interval (CI). A random effects model was used for the pooled analysis for all the outcome measures, including 1-year distant control rate, 1-year local control rate, 1-year survival rate, and complication. The consistency was tested by using node-splitting analysis and inconsistency standard deviation. The convergence was estimated according to the Brooks–Gelman–Rubin method.

A total of 12 literatures were included in this meta-analysis. WBRT+SRS showed higher 1-year distant control rate than SRS. WBRT+SRS was better for the 1-year local control rate than WBRT. SRS and WBRT+SRS had higher 1-year survival rate than the WBRT. In addition, there was no difference in complication among the three therapies.

Comprehensively, WBRT+SRS might be the choice of treatment for brain metastasis.

Abbreviations: CI = confidence interval, ISD = inconsistency standard deviation, MCMC = Markov chain Monte Carlo, PSRF = potential scale reduction factor, SRS = stereotactic radiotherapy, WBRT = whole brain radiotherapy.

Keywords: Bayesian network meta-analysis, brain metastasis, stereotactic radiotherapy, whole brain radiotherapy

1. Introduction

Brain metastasis is a common adult intracranial tumor; the overall incidence rate is about 8.3/100,000.[1,2] In clinic, about 21% to 83% of advanced cancer patients develop brain metastases.[2,3] The most common source of brain metastases are lung cancer, breast cancer, malignant melanoma, and gastrointestinal malignant tumors. There has been an increasing trend of the brain metastasis incidence[4] with the progress of medicine, improvement of treatment program for malignant tumor, and longer survival time.

Radiotherapy is still the main method for brain metastasis management due to the limited number of patients with indication for surgery.[5] Recently, the whole brain radiotherapy (WBRT) dominates the main strategies for the treatment of brain metastases, its effect, however, is unsatisfied because of the short median survival time, radiation resistance in some patients, and frequent complications.[6,7] Stereotactic radiosurgery (SRS) technology emerged in this context, and its therapeutic efficacy has been reported to be satisfactory and the complications are fewer, which makes it favored by clinicians.[8,9] Nevertheless, whether there is a need to plus SRS after WBRT remains controversial.[6,10,11]

There have been several related meta-analyses comparing the effects of WBRT, SRS, and/or WBRT+SRS in patients with brain metastasis,[12–15] which only focused on the comparison of WBRT+SRS with WBRT alone or SRS alone. To the best of our knowledge, no literature reports a comprehensive comparison of these 3 methods. In addition, important studies on this aspect have been published since then and might change the derived conclusions in the previous meta-analyses.[16–19] Therefore, this paper comprehensively compared these 3 methods (WBRT+SRS vs WBRT vs SRS) for the treatment of brain metastases by a network meta-analysis, with an expectation to provide a reference for the choice of treatment.

2. Methods

Ethical approval was not necessary as this study was a meta-analysis for relevant literatures all of which were separately approved by the ethics committee or institutional review board.

2.1. Search strategy

Electrical databases, PubMed and Embase, were searched for the relevant English papers regarding WBRT and SRS for the management of brain metastases. The keywords for retrieval were ("Brain metastases" OR "Brain metastasis" OR "brain

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metastatic tumor” OR “intracranial metastasis” OR “metastatic tumor of brain” OR “metastatic encephaloma”), (“whole brain radiotherapy” OR WBRT OR “whole brain irradiation” OR “whole brain radiation therapy”), and (“Stereotactic radiosurgery” OR “stereotactic radiotherapy”).

2.2. Inclusion criteria

The literature were selected according to the following criteria: English literature on the effects of WBRT, SRS, and/or WBRT+SRS in the treatment of brain metastases; the participants must be adults; at least one of the following indexes were reported, 1-year local control rate, 1-year survival rate, 1-year distant control rate, and complication; summary, report, commentary, and correspondence were excluded.

2.3. Data extraction

The following data were extracted independently by 2 investigators, including the first author, the year of publication, the year of study, the area of study, the total number of patients in each group, demographic characteristics (age and sex), 1-year local control rate, 1-year survival rate, 1-year distant control rate, and complication. If a dispute arised during the data extraction process, a panel discussion was held to reach a consensus with a 3rd investigator.

2.4. Statistical analysis

All the statistical analyses were performed by using ADDIS software (version 1.16.5). ADDIS software is a nonprogramming software based on the Bayesian framework and the priori evaluation and data processing using the Markov chain Monte Carlo algorithms.[20,21] Parameters for the ADDIS software were as follows: number of chains, 4; tuning iterations, 20,000; simulation iterations, 50,000; thinning interval, 10; inference samples, 10,000; and variance scaling factor, 2.5. Then, 1-year local control rate, 1-year survival rate, 1-year distant control rate, and complication were analyzed by network meta-analysis.

The effect sizes were odds ratio (OR) and 95% confidence interval (CI). A random effects model was used for the tests of all data. The consistency test was performed using the inconsistency standard deviation (ISD) and the node-splitting analysis, which is an alternative method to assess inconsistency in network meta-analysis. If the *P* value of the node-splitting analysis more than 0.05, a consistency model was used, otherwise, the non-consistency model was used.[22] Similarly, if the range of 95% CI of ISD includes, the consistency model was used otherwise the inconsistency model was used. For the closed-loop index, both node-splitting analysis and ISD were used to judge the consistency, while, for the open-loop indicators, ISD was used to test the consistency. The convergence of the model was determined by the potential scale reduction factor (PSRF) of the Brooks–Gelman–Rubin method[23]; PSRF closer to 1 indicated the better convergence; generally, PSRF less than 1.2 was acceptable.

3. Results

3.1. Literature selection

Literature search and screening process are shown in Fig. 1. With the predeveloped search strategy, 1388 iterature were retrieved from PubMed and Embase database. After removing the duplicates, 815 articles remained. By browsing the titles and abstracts, 689 articles were found to be incompatible with the inclusion criteria. Further, 114 articles were excluded after reading the full text. Finally, 12 articles were included.[16–19,24–31] The eligible studies were published from 1999 to 2016; the study area included Germany, Japan, the United States, and other countries or regions. There was no statistically difference in demographics characteristics (Table 1).

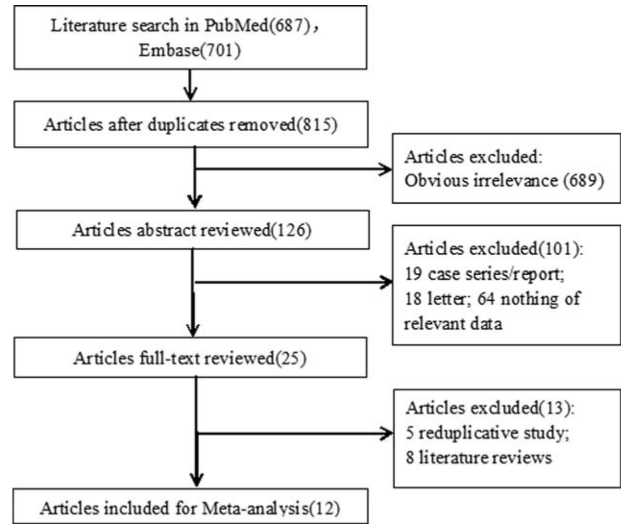

Figure 1. Flow chart for literature search and study selection. SRS = stereotactic radiosurgery, WBRT = whole-brain radiation therapy.

3.2. Network meta-analysis for the 1-year distant control rate

For 1-year distant control rate, the results of the ISD were OR = 0.91, 95% CI: 0.04 to 1.76. All the PSRFs were in the range of 1.00 to 1.01, which proved that the model was convergent and the result was stable. So, the consistency model was adopted. Figure 2A indicates that WBRT+SRS has the highest probability to rank 1 compared with WBRT or SRS alone. But on the whole there was no statistically significant difference between WBRT+SRS and WBRT (OR = 0.54, 95% CI: 0.14–1.92, Table 2).

3.3. Network meta-analysis for the 1-year local control rate

For 1-year local control rate, the consistency test was analyzed by using the ISD. The results were: OR = 1.60, 95% CI: 0.07 to 3.40, $P > .05$ (Table 3). The PSRFs were between 1.00 and 1.01, which proved that the model converged completely, the effect of iteration was very good and the result was stable, so the consistency model was adopted. Similar with Fig. 2A, B shows that WBRT+SRS has the highest probability to rank 1 compared with WBRT or SRS alone. But on the whole there was no statistically significant difference between WBRT+SRS and SRS (OR = 0.41, 95% CI: 0.13–1.04, Table 2).

3.4. Network meta-analysis for the 1-year survival rate

The insistency of studies for 1-year survival rate was analyzed by using the method of node-splitting analysis ($P > .05$, Table 4) and ISD (ISD: OR = 0.59; 95% CI: 0.02–1.68). All the PSRFs are in

Table 1

Characteristics of the included literature.

Author	Public year	Study year	Study location	Groups (intervention)	N	Age	M/F	1-year local control rate	1-year survival rate	1-year distant control rate	Complication
Kocher	2010	1996.11–2007.11	Germany	WBRT+SRS	99	NA	NA	80	36	67	NA
				SRS	100	NA	NA	69	35	51	NA
Andrews	2004	1996.1–2001.6	USA	WBRT+SRS	164	58.8 (19–82)	NA	134	46	NA	101*
				WBRT	167	59.9 (24–90)	NA	132	40	NA	102*
Aoyama	2006	1999.10–2003.12	Japan	WBRT+SRS	65	62.5 (36–78)	46/19	58	18	38	15
				SRS	67	62.1 (33–86)	53/14	46	26	27	10
Chang	2009	2001.1–2017.9	USA	WBRT+SRS	28	64 (40–78)	17/11	28	6	20	3
				SRS	30	63 (35–82)	12/18	20	19	14	1
Kondziolka	1999	NA	USA	WBRT+SRS	13	59 (46–74)	9/4	7	6	NA	NA
				WBRT	14	58 (33–77)	7/7	0	3	NA	NA
Rades	2007	1993–2005	Germany	WBRT	91	NA	47/44	24	21	60	NA
				SRS	95	NA	44/51	61	47	58	NA
Sneed	1999	1991.9–1997.2	USA	WBRT+SRS	43	50 (33–79)	NA	34	20	34	13
				SRS	62	63 (23–82)	NA	44	30	23	12
Rades	2008	1999–2007	Netherlands, USA, Germany	WBRT+SRS	51	NA	20/31	44	28	33	4
				SRS	93	NA	42/51	72	48	48	2
Brown	2016	2002.2–2013.12	North America	WBRT+SRS	102	61.4±10.6	55/46	24*	28	24	3
				SRS	111	59.8±10.4	54/57	12*	35	12	5
Aoyama	2015	1999–2014	Japan	WBRT+SRS	43	NA	NA	18	18	23	4
				SRS	45	NA	NA	16	14	23	9
Buglione	2015	2009.1–2013.12	Italy	WBRT+SRS	34	NA	NA	31	18	NA	NA
				WBRT	58	NA	NA	46	13	NA	NA
Halasz	2016	2007–2009	USA	WBRT	99	NA	54/45	NA	13	NA	NA
				SRS	90	NA	47/43	NA	27	NA	NA
Halasz	2016	1997–2009	USA	WBRT	75	NA	NA	NA	25	NA	NA
				SRS	42	NA	NA	NA	20	NA	NA

NA=not available, SRS=stereotactic radiosurgery, WBRT=whole-brain radiation therapy.
* Local and/or distant; M/F: male/female.

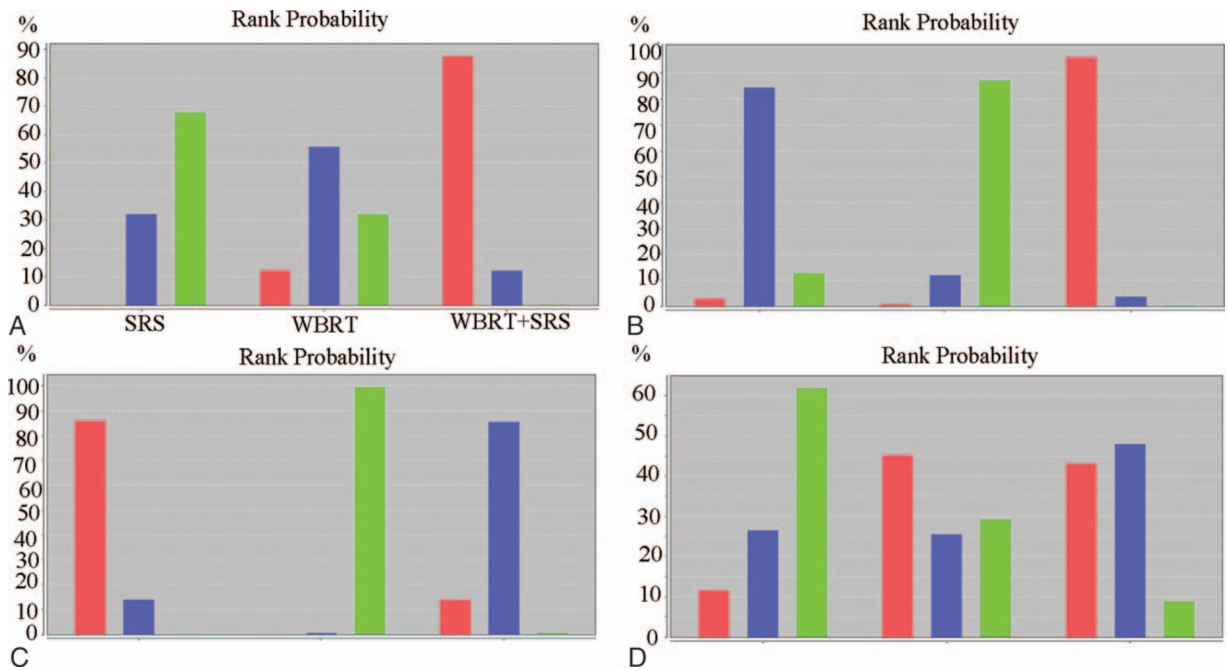

Figure 2. Rank probability diagram of the 1-year distant control rate (A), 1-year local control rate (B), 1-year survival rate (C), and complication (D).

the range of 1.00 to 1.01. It proved that the model converges completely, the effect of iteration is very good, and the result is stable, so the consistency model is adopted. As shown in Fig. 2C, SRS has the highest probability to rank 1 in the 1-year survival rates, but on the whole there was no statistically significant difference between WBRT+SRS and SRS (OR=1.22, 95% CI: 0.82–7.189, Table 2).

3.5. Network meta-analysis for the complication

Consistency of studies for complication was noted according to the results of ISD (OR=0.63, 95% CI: 0.03–1.23). All PSRFs between 1.00 and 1.01, indicating the convergence of the model was complete, so the consistency model was adopted. From Fig. 2D for complication, the difference among 3 groups was not statistically significant ($P>.05$, Table 2).

Table 2

Results for the network meta-analysis, OR (95%CI).

Name	1-year distant control rate	1-year local control rate	1-year survival rate	Complication
SRS, WBRT	0.80 (0.25, 2.75)	2.20 (0.46, 12.72)	2.54 (1.56, 4.58)	0.73 (0.14, 3.98)
SRS, WBRT+SRS	0.43 (0.26, 0.70)	0.41 (0.13, 1.04)	1.22 (0.82, 1.86)	0.73 (0.34, 1.56)
WBRT, WBRT+SRS	0.54 (0.14, 1.92)	0.19 (0.03, 0.71)	0.48 (0.27, 0.81)	0.97 (0.22, 4.39)

CI=confidence interval, OR=odds ratio, SRS=stereotactic radiosurgery, WBRT=whole-brain radiation therapy.

Table 3

Node-splitting analysis of the 1-year local control rate.

Name	Direct effect	Indirect effect	Overall	*P*
SRS, WBRT	−1.63 (−4.15, 1.10)	−0.11 (−2.46, 1.58)	−0.79 (−2.54, 0.77)	.29
SRS, WBRT+SRS	0.96 (0.05, 2.17)	−0.55 (−3.23, 3.12)	0.89 (−0.04, 2.07)	.30
WBRT, WBRT+SRS	1.03 (−0.22, 3.37)	2.56 (−0.03, 5.53)	1.67 (0.35, 3.42)	.28

SRS=stereotactic radiosurgery, WBRT=whole-brain radiation therapy.

Table 4

Node-splitting analysis of the 1-year survival rate.

Name	Direct effect	Indirect effect	Overall	*P*
SRS, WBRT	−0.96 (−1.71, −0.21)	−0.91 (−2.01, −0.05)	−0.93 (−1.52, −0.44)	.93
SRS, WBRT+SRS	−0.21 (−0.71, 0.25)	−0.28 (−1.26, 0.90)	−0.20 (−0.62, 0.20)	.88
WBRT, WBRT+SRS	0.68 (−0.02, 1.61)	0.78 (−0.17, 1.63)	0.73 (0.22, 1.32)	.86

SRS=stereotactic radiosurgery, WBRT=whole-brain radiation therapy.

4. Discussion

Compared with the previous reports of meta-analyses,[12–15] this study firstly used the network meta-analysis to comprehensively estimate the effects of WBRT, SRS, and WBRT+SRS for the treatment of brain metastasis. On the whole, WBRT+SRS should be the choice of treatment.

Controversial conclusions exist among different studies even among the reports of meta-analyses. Lv et al[15] evaluated the effects of WBRT with or without SRS and found that WBRT+SRS improved local tumor control rate and 1-year survival rate. Duan et al[12] compared the SRS with WBRT or without WBRT and found that SRS+WBRT has advantages in local recurrence and new brain metastasis rates, but SRS alone is associated with better neurological function. Tsao et al[13] respectively performed these 2 comparisons and concluded that although additional WBRT improves distant control and local control, SRS alone should be considered a routine treatment option due to favorable neurocognitive outcomes and less risk of late side effects. Except the studies those have been included in the previous studies, our study also included several new reported studies[16–19] which have been published during 2015 to 2016. Our study indicated that WBRT+SRS had higher 1-year distant control rate than SRS and higher 1-year local control rate than WBRT, as well as considerable 1-year survival rate and complications with SRS. Thus, the combined therapy should be recommended.

However, due to the limitations of the present study, the conclusion should be used critically. The inadequacies of this study included: covariates were not corrected because of the incomplete data in some studies; as confounding factors they may have a potential influence on the results of the meta-analysis; however, further subgroup analysis was not conducted; and although the ADDIS software is easy to use, it can be constrained by the fact that it cannot be programmed freely. For example, a random effects model can only be reported when estimating the effect size, which may be conservative in estimating our results.

In conclusion, WBRT+SRS may be a better method for the treatment of brain metastasis according to the comprehensive evaluation in this network meta-analysis.

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