

RESEARCH ARTICLE

Survival Outcomes after Whole Brain Radiation Therapy and/or Stereotactic Radiosurgery for Cancer Patients with Metastatic Brain Tumors in Korea: A Systematic Review

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Abstract

Aim: To compare survival outcomes after whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and WBRT plus SRS combination therapy in Korea, by performing a quantitative systematic review. **Materials and Methods:** We searched 10 electronic databases for reports on Korean patients treated with WBRT or SRS for brain metastases published prior to July 2010. Independent reviewers screened all articles and extracted the data. When a Kaplan-Meier survival curve was available, median survival time and standard errors were calculated. Summary estimates for the outcomes in each study were calculated using the inverse variance random-effects method. **Results:** Among a total of 2,761 studies, 20 studies with Korean patients (n=1,053) were identified. A combination of 12 studies (n=566) with WBRT outcomes showed a median survival time of 6.0 months (95% CI: 5.9-6.2), an overall survival rate of 5.6% (95% CI: 1-24), and a 6-month survival rate of 46.5% (95% CI: 37.2-56.1). For nine studies (n=412) on SRS, the median survival was 7.9 months (95% CI: 5.1-10.8), and the 6-month survival rate was 63.1% (95% CI: 49.8-74.8). In six studies (n=75) using WBRT plus SRS, the median survival was 10.7 months (95% CI: 4.7-16.6), and the overall and 6-month survival rates were 16.8% (95% CI: 6.2-38.2) and 85.7% (95% CI: 28.3-96.9), respectively. **Conclusions:** WBRT plus SRS showed better 1-year survival outcome than of WBRT alone for Korean patients with metastatic brain tumors. However, the results of this analysis have to be interpreted cautiously, because the risk factors of patients were not adjusted in the included studies.

Keywords: Neoplasm metastasis - brain - radiotherapy - radiosurgery - Korean patients

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Introduction

The diagnosis and treatment of brain tumors have improved recently, yet the number of patients with metastatic brain tumors continues to increase (Fox et al., 2011; Lichtor, 2013). Metastatic brain tumors occur in probably 25-35% of all cancer patients (Cairncross et al., 1980), although the exact number is not known. With the development of several new treatment methods, more cases are being actively treated.

Therapeutic options now include radiation therapy, surgery, chemotherapy, and combinations of these approaches. Radiation therapy may be administered as whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), or WBRT plus SRS. Since 1985, when SRS was introduced in Korea (NECA, 2011), the number of WBRT procedures for metastatic brain tumors has decreased, while the number of SRS procedures has increased in Korea. Nevertheless, radiation therapy

continues to be controversial, as does the optimum treatment for patients with metastatic brain tumors (Gwak, 2009).

The prognosis for a patient with a metastatic brain tumor is very poor, and thus the goals of treatment are to improve the quality of life and extend survival time. Several randomized clinical trials (RCTs) have been conducted, and median survival periods have been reported based on the type of radiation therapy (Kondziolka et al., 1999; Andrews et al., 2004; Aoyama et al., 2006; Chang et al., 2009). The reported median survival times are 5.7 (Andrews, Scott et al., 2004) and 7.3 (Kondziolka et al., 1999) months after WBRT, 15.2 (Chang et al., 2009) and 8.0 (Aoyama, Shirato et al., 2006) months after SRS, and 5.7 (Chang, Wefel et al., 2009) and 7.5 (Aoyama et al., 2006) months after WBRT plus SRS. However, there is still controversy over the optimal treatment of metastatic brain tumor and there is no evidence of survival outcomes according to radiation therapy in Korean patients. Thus,

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we conducted a systematic literature review and meta-analysis to estimate survival outcomes in Korean patients with metastatic brain tumors after WBRT, SRS, and WBRT plus SRS.

Materials and Methods

Literature search

We developed the protocol for a systematic literature review by considering population, intervention, comparison, and outcome (PICO) search methods, data extraction techniques, quality assessment, and meta-analysis. Searches of the literature published up to 29 June 2010 were performed in Ovid-Medline (1950-2010 week 25), Ovid-Embase (1950-2010 week 25), the Cochrane library (1950-2010 week 25), KoreaMed (<http://www.koreamed.org>), KISS (<http://kiss.kstudy.com>), KMBASE (<http://kmbase.medic.or.kr>), ndsl (<http://www.ndsl.kr>), KiSTi (<http://society.kisti.re.kr>), KOSTRO (<http://www.kostro.or.kr>), and JKNS (<http://jkns.or.kr>), using various combinations of MeSH headings and keywords such as “neoplasm metastasis,” “radiotherapy,” “radiosurgery,” “gamma knife,” “cyberknife,” “linac,” “whole brain radiotherapy,” “whole brain irradiation,” “stereotactic radiosurgery,” and “Korea” without restricting languages. Moreover, the references of all of the identified eligible articles were manually searched for additional relevant citations.

Study selection, data extraction, and quality assessment

Articles selected for the systematic review met all of the inclusion criteria: *i*) patients: all Korean patients with brain metastasis; *ii*) interventions: WBRT, SRS, or WBRT plus SRS combination therapy; *iii*) outcomes: median survival time, overall, 6-month, and 1-year survival rates; *iv*) timing: studies conducted since 1985, when SRS was introduced in Korea; and *v*) type of studies: all study designs except case reports.

Study selection, data extraction, and evaluation were performed independently by four reviewers (JEC, JHK, MKH, SYJ). The information entered on the data extraction form, designed specifically for this study, included study design, follow-up period, inclusion/exclusion criteria, sample size, gender and age of subjects, primary cancer, single/solitary/multiple tumors, recurrence, Karnofsky Performance Status (KPS), Eastern Clinical Oncology Group (ECOG) score, corresponding authors' affiliation, baseline characteristics, treatment protocol, and outcome variables. When more than one intervention (i.e., WBRT, SRS, WBRT plus SRS) was reported in a study, we extracted the data for each intervention.

Four reviewers (JEC, JHK, MKH, SYJ) evaluated the quality of each study using the Critical Guide to Case Series Reports (Carey and Boden, 2003), which contains eight items. Each study was graded on the basis of whether an item was present (+), absent (-), or unclear (?). Disagreements were decided by consensus, reached through discussion and negotiations. When consensus could not be reached, an outside party became involved, and the decisions were always based on the majority opinion.

Data collection process and meta-analysis

We performed a meta-analysis to synthesize the outcomes for each intervention. If overall, 6-month, or 1-year survival rates were not given in the text of the paper, but the data were presented in a bar chart or Kaplan-Meier curve, the survival rates were calculated from the graphic data. In case series, we calculated the survival rates directly when possible.

Standard errors of the median survival times are needed for meta-analysis; however, these were generally not provided in the articles. Therefore, we estimated the standard errors from the raw data or Kaplan-Meier curves, using a statistical equation (SPSS, 2007). In particular, for studies that presented a Kaplan-Meier curve, the median survival time and standard error calculations were performed according to a published method (Tierney et al., 2007). Two authors independently calculated the values and compared their results. In the case of a disagreement, both authors recalculated the results to reach an outcome.

We used a standard inverse variance meta-analysis to combine the outcomes of each study and obtain average effects and 95% confidence intervals (CI). We also report estimates from fixed and random effect models using an inverse-variance approach.

To assess heterogeneity across studies, we visually examined forest plots and used the Cochrane Q-statistic and I² statistic. Publication bias was assessed using funnel plots, the Begg and Mazumdar rank correlation (the Begg test), and Egger's linear regression asymmetry test of the intercept (the Egger test). When publication bias was suspected, we used the Duval and Tweedie nonparametric trim-and-fill method to obtain symmetry in the funnel plot and to determine the influence of hypothetical studies on the pooled estimate. We conducted the meta-analyses using Comprehensive Meta-analysis 2.0 (Biostat, Englewood, NJ).

Results

Search results

Figure 1 illustrates the process of selecting articles for inclusion in the systematic review and meta-analysis. Among 2,761 studies (346 from international databases and 2,415 from domestic Korean databases), 432 were duplicates; 2,310 were excluded; and one additional study was identified by searching references. Finally 20 studies (n=1,053) were identified. Five of the 20 studies reported the outcomes of two types of interventions, and one study reported on WBRT, SRS, and WBRT plus SRS (see Table 4). Thus, the meta-analysis included 12 studies (n=566) on WBRT, nine studies (n=412) on SRS, and six studies (n=75) on WBRT plus SRS. A summary of the included studies is presented in the Appendix. Fifteen (75%) of the studies were published since 2000, and the corresponding authors' affiliation was neurosurgery in 45% of these. All of the SRS-related studies were published since 2003, and the corresponding author's affiliation was neurosurgery in most of these.

Meta-analysis

We performed a meta-analysis by intervention and

outcomes. The results of the meta-analysis of radiation therapy for each outcome in brain metastasis patients are summarized in Table 1. Table 2 shows the results of tests for publication bias.

Whole brain radiation therapy

Median survival period after WBRT was estimated as 6.0 months (95%CI: 5.9-6.1) by combining four studies (n=104). Overall survival after WBRT was estimated as 5.5% (95%CI: 1.1-23.7) by combining two studies (n=32); 6-month survival was estimated as 46.5% (95%CI: 37.2-56.1) by combining nine studies (n=365); and 1-year survival was estimated as 27.95% (95%CI: 19.8-37.8) by combining nine studies (n=360; Figure 2).

The median survival months and overall survival showed no evidence of statistical heterogeneity among the studies (overall survival: I²=0, p=0.343; median survival month: I²=0, p=0.084). However, the 6-month and 1-year survival rates exhibited some evidence of statistical heterogeneity among the studies (6-month survival:

I²=57.7, p=0.015; 1-year survival: I²=60.8, p=0.009), and thus we employed a random effect model to test for significance.

Stereotactic radiosurgery

Median survival after SRS was estimated as 7.9 months (95%CI: 7.9-8.1) by combining eight studies (n=171). The 6-month survival rate was estimated as 63.1% (95%CI: 49.8-74.8) by combining five studies (n=325), and 1-year survival was estimated as 34.3% (95%CI: 23.2-47.6) by combining four studies (n=339; Figure 3).

In all outcomes, there was evidence of statistical heterogeneity among the studies (median survival month: I²=99.84, p<0.001; 6-month survival: I²=68.4, p=0.013; 1-year survival: I²=68.5, p=0.023). Thus, we used a random effect model.

As publication bias was suspected in the SRS 6-month survival (Table 2), we conducted a trim-and-fill analysis, which yielded a 6-month survival estimate of 54.9%

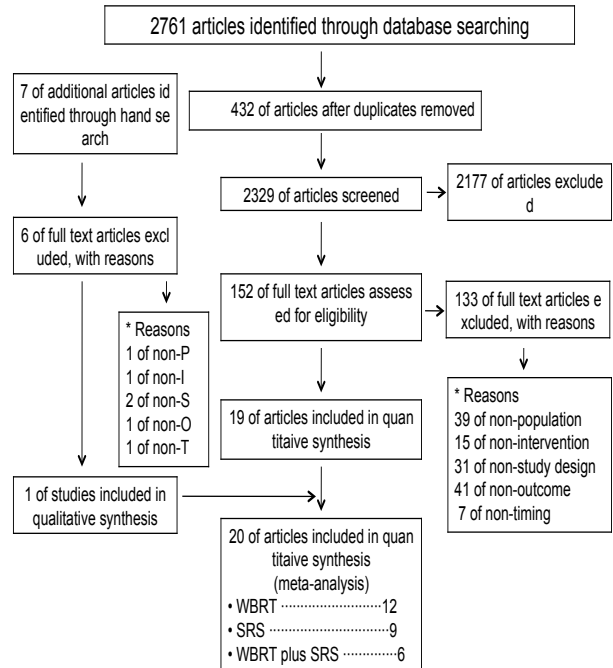


Figure 1. Study Flow Diagram

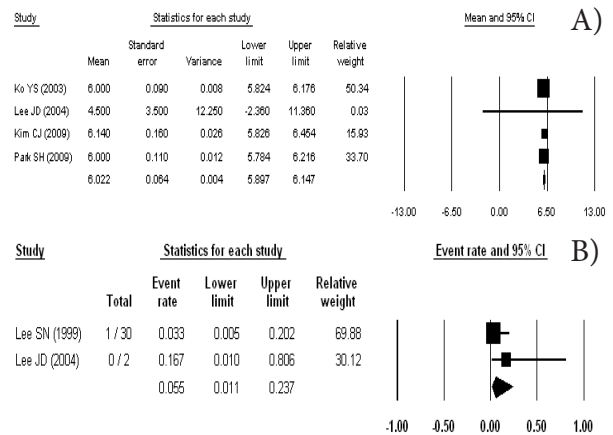


Figure 2. Outcomes after Whole Brain Radiation Therapy. A) Median survival; B) Overall survival; C) 6-month survival; and D) 1-year survival

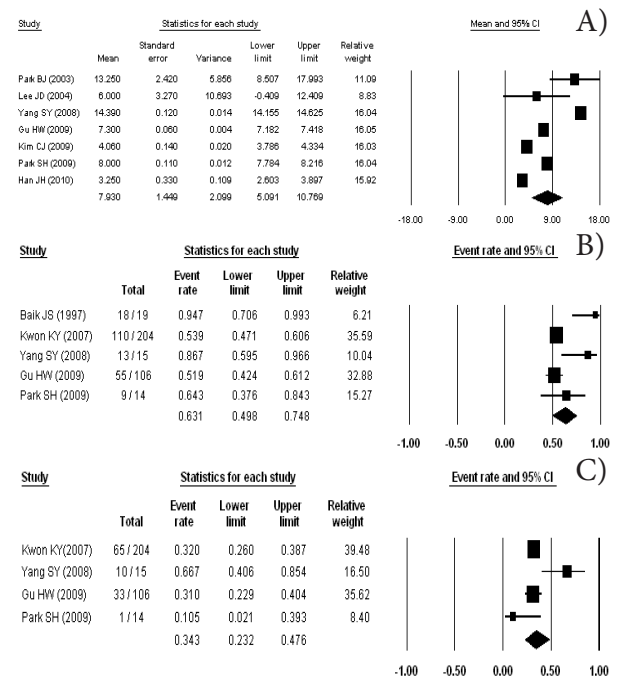


Figure 3. Outcomes after Stereotactic Radiosurgery. A) Median survival; B) 6-month survival; and C) 1-year survival

Table 1. Meta-analysis of Radiation Therapy for Each Outcome in Patients with Brain Metastases

Intervention	Outcome	No. of Studies	No. of Patients	Model	Point estimate	95%CI	I ² , %	Heterogeneity p value
WBRT	Median survival, months	4	104	I-V, F-M	6.022	5.897-6.147	<0.001	0.842
	Overall survival	2	32	I-V, F-M	0.055	0.011-0.237	0	
	6-month survival	9	365	I-V, R-M	0.465	0.372-0.561	57.702	
	1-year survival	9	360	I-V, R-M	0.279	0.198-0.378	60.827	
SRS	Median survival, months	8	171	I-V, R-M	7.93	5.091-10.769	99.849	0
	6-month survival	5	325	I-V, R-M	0.631	0.498-0.748	68.433	
	1-year survival	4	339	I-V, R-M	0.343	0.232-0.476	68.501	0.023
WBRT+SRS	Median survival, months	4	35	I-V, R-M	10.669	4.721-16.617	97.066	0
	Overall survival	4	27	I-V, F-M	0.168	0.062-0.382	<0.001	0.484
	6-month survival	2	48	I-V, R-M	0.857	0.283-0.989	83.826	0.013
	1-year survival	2	48	I-V, R-M	0.718	0.429-0.896	70.51	0.066

*Abbreviations: WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; WBRT+SRS, WBRT plus SRS combination therapy; Pts, Patients, I-V, inverse-variance method; F-M, fixed model; R-M, random model; CI, confidence interval

Table 2. Tests for Publication Bias

Intervention	Outcome	Egger Test p value	Begg Test p value
WBRT	Median survival, months	0.857	1
	6-month survival	0.076	0.917
	1-year survival	0.068	0.466
SRS	Median survival, months	0.998	0.764
	6-month survival	0.032	0.086
	1-year survival	0.865	0.734
WBRT+SRS	Median survival, months	0.595	0.734
	Overall survival	0.844	0.734

*Abbreviations: WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; WBRT+SRS, WBRT plus SRS combination therapy

Table 3. Comparison of Median Survival (months) of Korean Patients Compared with Other Countries

Study	Study design	WBRT	SRS	WBRT plus SRS
This study		6	7.9	10.7
Kondziolk et al. (1999)	RCT	7.5		11
Sneed et al. (1999)	RC		11.3	11.1
Chidel et al. (2000)	RC		10.5	6.4
Hoffman et al. (2001)	RC		13.9	14.5
Sneed et al. (2002)	RC		7.2	8.6
Noel et al. (2003)	RC		7	14
Andrews et al. (2004)*	RCT	5.7		6.5
Combs et al. (2004)	RC		9	6
Datta et al. (2004)	RC	6		6
Aoyama et al. (2006)	RCT		8	7.5
Rades et al. (2007)	RC	7	13	
Chang et al. (2009)	RCT		15.2	5.7
Lee et al. (2008)	RC	6	29	

*Mean survival (months); **Abbreviations: WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; WBRT+SRS, WBRT plus SRS combination therapy; RCT, randomized clinical trial; cohort, RC, retrospective cohort

(95%CI: 39.1-69.8) when two studies were excluded. This estimate was not significantly different from the original estimate (63.1%).

Whole brain radiation therapy plus stereotactic radiosurgery

Median survival after WBRT plus SRS was estimated as 10.7 months (95%CI: 11.6-12.1) by combining four studies (n=35), and overall survival was estimated as 16.8% (95%CI: 6.2-38.2) by combining four studies (n=27). The 6-month and 1-year survival rates were

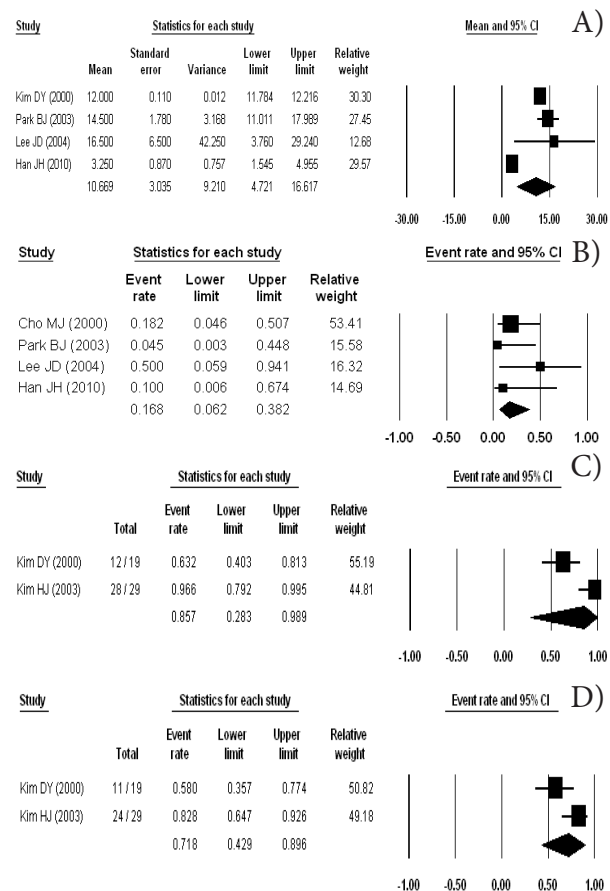


Figure 4. Outcomes after Whole Brain Radiation Therapy Plus Stereotactic Radiosurgery. A) Median survival; B) 6-month survival; C) 6-month survival; and D) 1-year survival

estimated as 85.7% (95%CI: 23.8-98.9) and 71.8% (95%CI: 42.9-89.6), respectively, by combining two studies (n=48) for each. The wide confidence intervals in both cases are attributable to the inclusion of only two studies.

There was no evidence of statistical heterogeneity in overall survival among the studies (I²=0, p=0.484). However, because there was evidence of statistical heterogeneity in the other outcomes (median survival month: I²=97.1, p<0.001; 6-month survival: I²=83.8, p=0.013; 1-year survival: I²=70.5, p=0.066), we used a random effect model.

Table 4. Summary Table of Included Studies

Study	Enrollment period	Affiliation of corresponding author	Intervention (n)			Outcome (Y/N)			
			WBRT	SRS	WBRT+SRS	Overall survival	6-month survival	1-year survival	Median survival (M)
Hong SE (1994)	1991~1993	Radiation Oncology	24					Y	Y
Baik JS (1997)	1992.1~1995.12	Neurology	165	19				Y	
Jang SS (1998)	1994.1~1997.4	Therapeutic Oncology	33					Y	Y
Lee SN (1999)	1987.1~1998.1	Internal Medicine	30				Y	Y	Y
Yoo H (1999)	1987~1994	Neurosurgery	25					Y	Y
Cho MJ (2000)	1997.8~1998.12	Therapeutic Oncology			11		Y		
Kim DY (2000)	1995.10~1998.2	Therapeutic Oncology			19	Y		Y	Y
Kim CS (2002)	1985.1~1998.3	Neurosurgery	15					Y	Y
Kim HJ (2003)	1996.10~2002.2	Therapeutic Oncology			29			Y	Y
Kim IK (2003)	1993.1~2002.9	Surgery	10					Y	Y
Ko YS (2003)	1998.1~2003.1	Neurosurgery	44			Y		Y	Y
Park BJ (2003)	1996.1~2000.12	Neurosurgery		15	10	Y	Y		
Lee JD (2004)	1986.3~2003.5	Surgery	2	3	2	Y	Y		
Kwon KY (2007)	2002.1~2005.10	Neurosurgery		204				Y	Y
Yang SY (2008)	1998.1~2005.12	Neurosurgery		15		Y		Y	Y
Gu HW (2009)	2000.11~2008.4	Neurosurgery		106		Y		Y	Y
Gwak HK (2009)	2001.1~2008.1	Radiation Oncology	160						Y
Kim CJ (2009)	2004.1~2006.12	Radiation Oncology	39	29		Y			
Park SH (2009)	2005.1~2006.12	Neurosurgery	19	14		Y		Y	Y
Han JH (2010)	1991~2007	Neurosurgery		7	4	Y	Y		

*Abbreviations: WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; WBRT+SRS, WBRT plus SRS combination therapy

Discussion

This study is the first reported quantitative systematic review of survival outcomes after radiation therapy in Korean patients with metastatic brain tumors. After WBRT, 1-year survival rate was 5.6%, and after WBRT plus SRS, 1-year survival was 71.8%. Without overlapping of the CI, WBRT plus SRS showed better 1-year survival outcome than of WBRT alone for Korean patients with metastatic brain tumors. However, the results of this analysis have to be interpreted cautiously, because the risk factors of patients are not adjusted in the included studies.

Table 3 shows the median survival times after radiation therapy in patients with brain metastases reported in studies contained in a recently published systematic review (Linskey et al., 2010; Patil et al., 2010). The ranges of the median survival times reported in all of the studies were 5.7-7.5, 7.0-29.0, and 5.7-14.5 months after WBRT, SRS, and WBRT+SRS, respectively. The median survival ranges reported for the retrospective cohorts were 6.0-7.0, 7.0-29.0, and 6.0-14.5 months, after WBRT, SRS, and WBRT+SRS, respectively. In our study, the pooled estimates for each treatment were within these ranges. In other words, the median survival of radiation therapy in Korean patients with metastatic brain tumors was within the ranges reported from other countries.

Fifteen (75%) of the studies were published since 2000, and the affiliation of the corresponding author was neurosurgery in 45% of these (Table 4). Additionally, all SRS reports were published since 2003, and the corresponding author's affiliation was neurosurgery in most of these (Table 4).

We extracted available data from all reported observational cohort studies, even though there was no formal RCT. In some studies, survival outcomes were presented only in graphic form, and great effort was made to calculate survival rates from the graphs, bar charts, and

Kaplan-Meier curves, according to a published method (Tierney et al., 2007). To evaluate the accuracy of the analyses, two authors independently processed the same data and compared findings, which were recalculated as necessary. Through this process, a large amount of information was gathered from many studies and was used to determine current survival outcomes in Korean patients.

Our study has several limitations. First, the survival outcomes of the different types of radiation therapy difficult to compare at the same level, because we performed a one-arm meta-analysis. But, we can be found statistical difference based on intersection of CI, and WBRT plus SRS showed better 1-year survival rate than of WBRT alone. Second, quality of life is very important outcomes for metastatic brain tumor patients. But we analyzed only the survival outcome of each intervention and did not consider quality adjusted life year, because we did not find a relevant study that reported outcomes. Third, metastatic brain tumors are very heterogeneous disease with varied risk factors (i.e. the primary tumor site, the number of metastasis, history of previous treatment, patients' functional status, etc). But, we couldn't analyzed based on risk factors, because we did not find a reported outcome stratified by varied risk factors, after whole brain radiation therapy and/or stereotactic radiosurgery for cancer patients with metastatic brain tumors. Fourth, the included studies were all observational studies, and there was evidence of statistical heterogeneity in some outcomes. Although we performed subgroup and sensitivity analyses, we were unable to resolve the heterogeneity. Patients with metastatic brain tumors differ in terms of the severity of the primary cancer, the site of metastasis, the number of brain metastases, and general health condition. Therefore, their treatment is not uniform. Furthermore, medical teams rightly use every possible treatment method to increase life expectancy for these patients, making a well-designed RCT impossible for metastatic brain tumor patients. The

observational studies used were based on patients in actual medical practice, and thus despite their limitations, these studies reflect real-world circumstances. In that sense, our study is meaningful.

In conclusion, we determined the survival outcomes after WBRT, SRS, and WBRT plus SRS for Korean patients with metastatic brain tumors. The pooled estimates for each treatment were within the ranges reported in studies from other countries. And WBRT plus SRS showed better than of WBRT alone in 1-year survival outcome for Korean patients with metastatic brain tumors. However, the results of this analysis have to be interpreted cautiously, because the risk factors of patients are not adjusted in the included studies.

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