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Patients with Single Brain Metastasis from Non-Small Cell Lung Cancer Equally Benefit from Stereotactic Radiosurgery and Surgery: A Systematic Review

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Background: The appropriate treatment of non-small cell lung cancer (NSCLC) with single brain metastasis (SBM) is still controversial. A systematic review was designed to evaluate the effectiveness of neurosurgery and stereotactic radiosurgery (SRS) in patients with SBM from NSCLC.





Material/Methods: PUBMED, EMBASE, the Cochrane Library, Web of Knowledge, Current Controlled Trials, Clinical Trials, and 2 conference websites were searched to select NSCLC patients with only SBM who received brain surgery or SRS. SPSS 18.0 software was used to analyze the mean median survival time (MST) and Stata 11.0 software was used to calculate the overall survival (OS).

Results: A total of 18 trials including 713 patients were systematically reviewed. The MST of the patients was 12.7 months in surgery group and 14.85 months in SRS group, respectively. The 1, 2, and 5 years OS of the patients were 59%, 33%, and 19% in surgery group, and 62%, 33%, and 14% in SRS group, respectively. Furthermore, in the surgery group, the 1 and 3 years OS were 68% and 15% in patients with controlled primary tumors, and 50% and 13% in the other patients with uncontrolled primary tumors, respectively. Interestingly, the 5-year OS was up to 21% in patients with controlled primary tumors.

Conclusions: There was no significant difference in MST or OS between patients treated with neurosurgery and SRS. Patients with resectable lung tumors and SBM may benefit from the resection of both primary lesions and metastasis.

MeSH Keywords: **Brain Neoplasms • Carcinoma, Non-Small-Cell Lung • Craniotomy • Radiosurgery • Review**

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Background

Lung cancer is one of the leading causes of death worldwide [1,2], and non-small cell lung cancer (NSCLC) accounts for 80% to 85% of this kind of malignancy [3]. Brain metastases are common in patients with lung cancer and reach a rate of approximately 30% to 50% [4,5], about half of which are single brain metastasis (SBM) [6]. Currently, more and more brain metastases are found in NSCLC patients [7,8], and patients with brain metastasis are usually considered to be terminal stage and to have poor prognosis. The median survival time (MST) of NSCLC patients with brain metastases is 1~2 months in patients without any treatment and 4 to 6 months in patients that received radiotherapy, respectively [9,10]. Unlike the patients with multiple brain metastases, patients with SBM exhibit a potential to improve the duration (exceeding 1~2 years) and quality of life [11].

The current methods for treatment of NSCLC patients with SBM are neurosurgery, stereotactic radiosurgery (SRS), and whole-brain radiotherapy (WBRT) [12]. However, the standard treatment schedule for these patients is still unclear. Many researches had investigated the appropriate treatment for NSCLC patients with SBM, with the conclusion that local tumor control rates were similar between surgery and SRS in selected patients [13]. Patients with SBM who received surgical resection or SRS combined with WBRT had better overall survival (OS) and quality of life compared to those treated with WBRT alone [14–16]. Some researcher believe that postoperative WBRT may reduce the recurrence of cancer in the brain, but surgical resection or SRS alone may provide an equivalent survival advantage and less deterioration of neurocognitive functions compared with surgery or SRS plus WBRT [17,18]. In addition, neurosurgery provided longer survival time than SRS or other form of conservative management [19,20]. Which is better, surgery or SRS? To answer the question, systematic review and analysis of the survival data related to different treatments of these patients is necessary.

Currently, there is still no prospective randomized clinical trial comparing surgical resection with SRS for patients with SBM from NSCLC. In this study, we performed a systematic review to evaluate the MST and OS of patients with SBM from NSCLC who received surgical resection and SRS.

Material and Methods

Search strategy

We searched PubMed, EMBASE, the Cochrane Library, Web of Knowledge, Current Controlled Trials, Clinical Trials, 2 conference websites (the American Society for Radiation Oncology

(ASTRO), and the American Society of Clinical Oncology (ASCO) for relevant articles published up to April 1, 2014. We scrutinized the reference lists from the selected papers for any other additional studies and limited studies to those written in English. Mesh and text word searches were undertaken in PUBMED, EMBASE, and Cochrane Library databases, including the following: 'lung neoplasms', 'brain neoplasms', 'lung tumor', 'brain metastases', 'surgery', and 'radiosurgery'; text word searches were conducted in the other databases using the search terms 'lung cancer', 'brain metastases', 'surgery', and 'radiotherapy'.

Inclusion criteria

1. Types of studies: randomized controlled trials, clinical control trials, cohort study, and retrospective case series concerning neurosurgery or SRS for SBM from NSCLC. 2. Types of participants: among the selected patients, NSCLC were histologically diagnosed, and brain metastases were confirmed by histological examination, magnetic resonance imaging (MRI), or enhanced computed tomography (CT) scan. 3. Types of interventions: surgery with or without WBRT or SRS (including gamma knife radiosurgery) with or without WBRT. 4. Outcome measures: median survival time (MST) and overall survival (OS).

Exclusion criteria

1. Patients with multiple brain metastases, small-cell lung cancer, solitary brain metastasis from other primary malignancies. 2. NSCLC patients with multiple organ metastases were excluded. 3. Studies of the palliative therapy such as WBRT alone or chemotherapy alone were excluded. 4. Articles with no eligible data were excluded.

Study selection

Eligibility assessment was first performed by screening titles and abstracts, and further assessment was performed by reviewing the full text. All of the eligible articles were selected by 2 reviewers (Qin and Wang) according to the inclusion and exclusion criteria. Disagreement on article inclusion was solved by discussion.

Data collection

All studies were evaluated by 2 reviewers (Qin and Wang) to assess whether the studies matched the inclusion criteria. There were no updated studies. The following information was abstracted from all eligible studies: title, authors, publication time, number of cases, male-to-female ratio, average age, performance status, pathological types, and tumor node metastasis (TNM) stage; treatment of metastases, treatment of primary lung cancer, and outcomes (MST and overall survival rate).

Quality assessment

In this review, all included studies are non-randomized controlled trials, and most of them are non-comparative studies. Few validated instruments are available to determine the methodological quality of observational or non-comparative studies. Finally, the Methodological Index for Non-Randomized Studies (MINORS) [21] was used to assess the quality of eligible studies. MINORS is a valid instrument designed to assess the methodological quality of non-randomized studies, whether comparative or non-comparative which contained 12 items, the first 8 being specifically for non-comparative studies, whereas all 12 items are relevant to comparative studies. Each item is scored 0 (not reported), 1 (reported but inadequately), and 2 (reported adequately). The ideal global score would be 16 for the non-comparative studies and 24 for the comparative studies. Two reviewers (Qin and Wang) independently evaluated and cross-checked quality of the studies.

Statistical analysis

SPSS 18.0 statistical software was used to analyze the MST of each group. Stata 11.0 software was used to calculate single-sample rate meta-analyses to determine the survival rate of each group. Chi-square and I-square tests were used to test heterogeneity amongst the studies. The significance threshold of chi-square was set at $\alpha=0.1$, it was deemed that heterogeneity existed when $P<0.1$. I^2 was used to quantify the heterogeneity across trials and to assess the impact of heterogeneity on the meta-analysis; the value was more than 50% considerable heterogeneity. The OS was estimated using a fixed-effects model if there was no heterogeneity; otherwise the random-effects model was used.

Results

A total of 18 articles are included in our final study after reviewing a total of 2280 selected articles. All studies were observational. There were 2 clinical control studies (Hu, C. S. 2006 Li, H. 2009), 16 retrospective case series, and no randomized controlled trials. The screening process and results of the literature are presented in Figure 1.

General characteristics of the eligible studies

There were 713 patients among the 18 studies between 1976 and 2011 (Table 1), including 7 patients with 2 brain metastases and 1 patient with 3 brain metastases. According to the different treatments for brain metastases, 16 eligible studies were included in the surgery group and 4 studies in the SRS group. Data from the 2 clinical control trials are distributed to the surgery and SRS group (e.g., Hu, C. S. et al. (part), Li, H. et

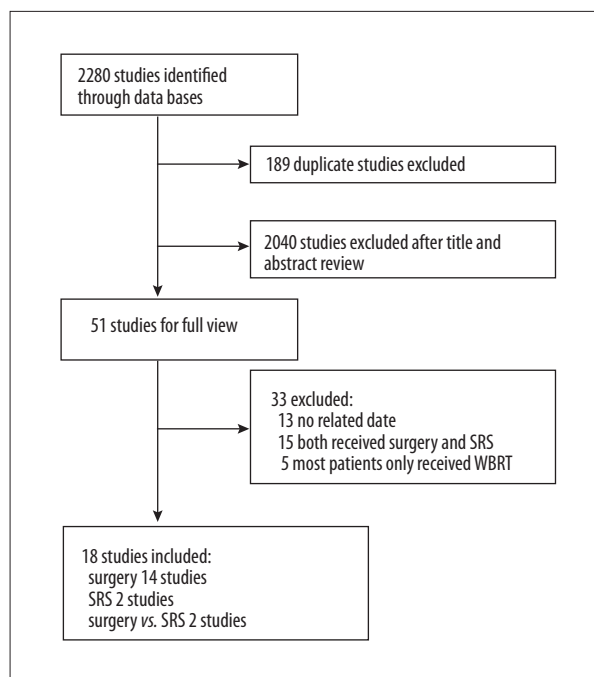


Figure 1. A flow chart of selecting trials included in the meta-analysis.

al. (part) in Table 1.). For subgroup analysis, the surgery group was divided into a “controlled” primary subgroup (all the participants in this trial with complete resection of the primary lung tumor) and an “uncontrolled” primary subgroup (not all the patients received resection of the primary lung tumor (i.e., some with palliative radiotherapy, chemotherapy, or no treatment), which contained 9 studies and 7 studies, respectively.

The MST range of the patients in the surgery group was 5.5–27.8 months and in the SRS group it was 7.4–18 months. The 1-year, 2-year, and 5-year survival rates ranged from 21–90%, 28–48.8%, and 8.3–37% in the patients treated with surgery, and 44.8–71.3%, 32.6–34.1%, and 10.4–21% in the patients treated with SRS. In the 18 eligible studies, 12 studies reported survival outcomes from the time of craniotomy or lung surgery, 3 studies reported survival from the time of diagnosis of brain metastasis or lung cancer, and 3 studies did not clearly define how survival outcomes were measured.

The basic characteristics of each group

The basic characteristics of the 2 groups are presented in Table 2. There were 550 cases in the surgery group, and 163 cases in the SRS group. The average age was 55.5 years and 59.7 years, respectively. All of the participants exhibited good performance status ($PS \geq 70$). The male/female ratios were 3: 1 in the surgery group and 2: 1 in the SRS group. The pathological types in the surgery group were adenocarcinoma (53.5%), squamous cell carcinoma (25.1%), large-cell carcinoma (5%),

Table 1. General characteristics of the eligible studies.

Studies	Years	Groups	Cases	Average ages	MST	OS	MINORS score	
Tummarello, D. et al.	1985	Surgery**	15	49 y	6 M	–	11	
Saitoh, Y. et al.	1999	Surgery*	24	57.8 y	6.8 M	3-year 5-year	12.5% 8.3%	12
Mussi, A. et al.	1985	Surgery*	20	50.5 y	–	5-year	33.6%	10
Macchiarini, P. et al.	1991	Surgery*	37	56 y	27 M	5-year	37.0%	10
Louie, A. V. et al.	2009	Surgery**	35	58.5 y	7.8 M	–	–	14
Granone, P. et al.	2001	Surgery*	30	58.7 y	27.8 M	1-year 2-year 3-year	80.0% 41.0% 17.0%	11
Catinella, F. P. et al.	1989	Surgery*	12	–	–	1-year 4-year	90.0% 56.0%	8
Bai, H. et al.	2011	Surgery**	18	54 y	12.8 M	1-year 2-year 3-year	83.3% 48.8% 13.9%	11
Wang, Z. M. et al.	2002	Surgery**	32	55.8 y	12 M	1-year	40.6%	12
Mussi, A. et al.	1996	Surgery*	45	56.9 y	19 M	5-year	16.0%	13
Magilligan, D. J., Jr.	1987	Surgery*	41	–	13 M	1-year 2-year 4-year 5-year	55.0% 31.0% 21.0% 21.0%	10
Magilligan, D. J., Jr.	1976	Surgery*	22	54.8 y	14 M	1-year	45.0%	9
Bonnette, P.	2001	Surgery**	103	54 y	12.4 M	1-year 2-year 3-year 4-year	56.0% 28.0% 13.0% 11.0%	14
Ampil, F. et al.	2007	Surgery**	28	–	5.5 M	1-year	21.0%	16
Hu, C. S. et al. (part)	2006	Surgery**	53	60 y	12 M	–	–	23
Li, H. et al. (part)	2009	Surgery*	35	–	13 M	–	–	22
Flannery, T. W. et al.	2008	SRS	42	58 y	18 M	1-year 2-year 5-year	71.3% 34.1% 21.0%	12
Flannery, T. W. et al.	2003	SRS	72	58 y	15.7 M	1-year 2-year 5-year	61.4% 32.6% 10.4%	12
Hu, C. S. et al. (part)	2006	SRS	31	63 y	7.4 M	–	–	23
Li, H. et al. (part)	2009	SRS	18	–	14 M	1-year	44.8%	22

Surgery* – subgroup of surgery which had controlled primary tumor; surgery** – subgroup of surgery which had uncontrolled primary tumor.

and others (16.4%). The T status of the primary tumor in the surgery group was classified as T1-2, and only 2 participants were stage T4. With respect to the N stages in the surgery group, there were 151 patients in N0 stage, 35 patients in N1 stage, 60 patients in N2 stage, and 1 patient in N3 stage. In the SRS group, only N stages were acquired. Furthermore, in

the surgery group, approximately 39.6% of patients received WBRT, 71.6% of patients underwent resection of the lung lesion, and 20.5% of patients underwent thoracic radiotherapy. In the SRS group, the number of patients who received WBRT, lung lesion resection, and thoracic radiotherapy were 47.9%, 10.4%, and 8.6%, respectively.

Table 2. The basic characteristics of each group.

		Surgery group	SRS group
Total number		550	163
Average ages		55.5 y	59.7 y
Male: female		331: 103	96: 49
S: M*		101: 76	81: 33
Pathological	ADC*	196	–
	SCC*	103	–
	LC*	17	–
T stage	T1–2	201	–
	T3	55	–
	T4	2	–
N stage	N0	151	20
	N1	35	6
	N2	60	–
	N3	1	–
WBRT		218	78
Thoracic surgery		394	17
Thoracic radiotherapy		113	14

S: M – synchronous versus metachronous brain metastasis; ADC – adenocarcinoma; SCC – squamous cell carcinoma; LC – large cell carcinoma.

Quality of studies

MINORS was used to assess all the included studies. The scores range from 8 to 16 for the non-comparative studies and 22 to 23 for the comparative studies (Table 1), which demonstrated a moderate methodological heterogeneity of the studies included.

Mean survival time (MST) and survival rate

The MST of surgery and SRS were 12.7 months and 14.85 months, respectively (Figure 2). In the surgery group, 2 studies did not report the MST, and statistical analysis was only conducted on 14 studies.

The 1-year, 2-year, and 5-year OS were 59%, 33%, and 19% in the surgery group, and 62%, 33%, and 14% in the SRS group, respectively (Figure 3). Based on the above data, we concluded that there was no significant difference between the surgery and SRS group, and that neurosurgery tends to confer longer survival. In addition, the 1-year, 3-year, and 5-year OS of complete resection of the lung lesions combined with craniotomy in the surgery group were 68%, 15%, and 21%, and

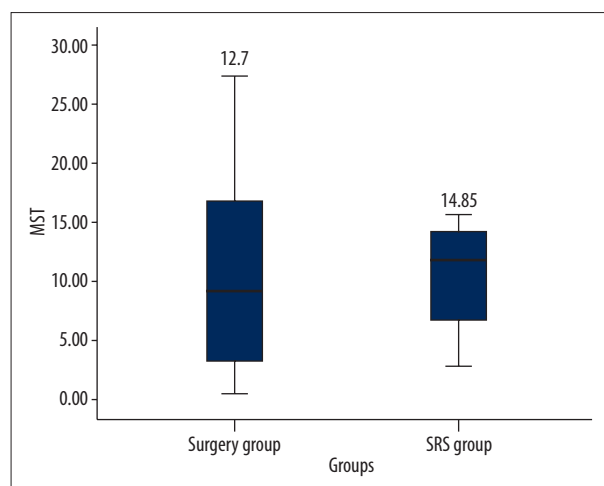


Figure 2. The MST of the patients was 12.7 months in surgery group and 14.85 months in SRS group.

the 1-year and 3-year OS of patients with uncontrolled primary lung cancer in the surgery group were 50% and 13%, respectively (Figure 4). Therefore, the resection of the primary tumor and SBM is worthwhile for patients.

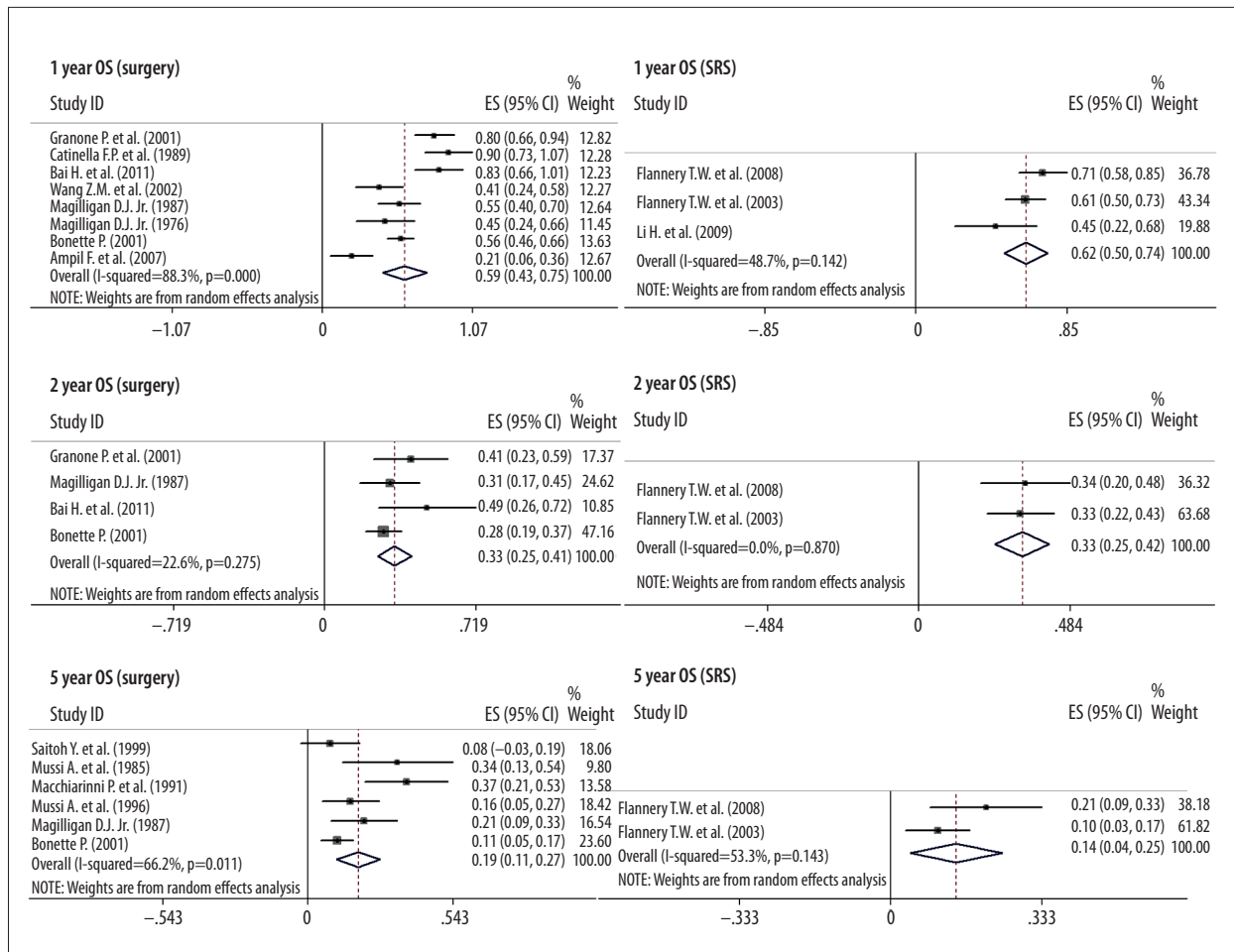


Figure 3. The 1-, 2-, and 5-year OS of the patients were 59%, 33%, and 19% in surgery group, and 62%, 33%, and 14% in SRS group, respectively.

Furthermore, in surgery group, most studies published before the year 2000, and all studies in the SRS group, were published after 2000. Over the last 2 decades, the survival of NSCLC has been improving enormously owing to the progress of systemic therapy. Therefore, when we excluded the studies published before 2000, and reanalyzed the MST and OS in the surgery group, the results showed that the MST was 12.2 months, and the 1-and 2-year OS was 56% and 36%.

Discussion

In our systematic review and meta-analysis, both surgical resection and SRS are believed to be an effective treatment for patients with SBM from NSCLC, and there is no significant difference between effectiveness of surgery and SRS. In the subgroup analysis, combined excision of the primary tumor and the metastasis can achieve a 5-year survival rate up to 21%, which indicates that controlling the primary tumor is associated with better survival in patients with SBM.

WBRT was first reported for treatment of brain metastases in the mid-1950s, and it has long remained a fundamental treatment for patients with brain metastases to improve survival time. In the 1990s, 2 prospective randomized trials [14,15] illustrated that in patients with SBM, surgical resection followed by WBRT improved overall survival and quality of life compared with WBRT alone, which established the role of surgical techniques in the management of brain metastases. Surgical resection was mainly recommended for patients with SBM in an accessible location, especially for those with good functional status and absent or controlled systemic disease.

SRS delivers focused high-dose radiation to a small area and avoids significant damage to the surrounding tissue, which is particularly useful in patients who are not candidates for surgery or with lesions in non-resectable locations [22]. One study (RTOG 9508) showed a survival benefit of SRS plus WBRT over WBRT alone (6.5 months versus 4.9 months, respectively; $P=0.0393$) in patients with SBM, which greatly contributed to the increased use of SRS for treatment of brain metastases

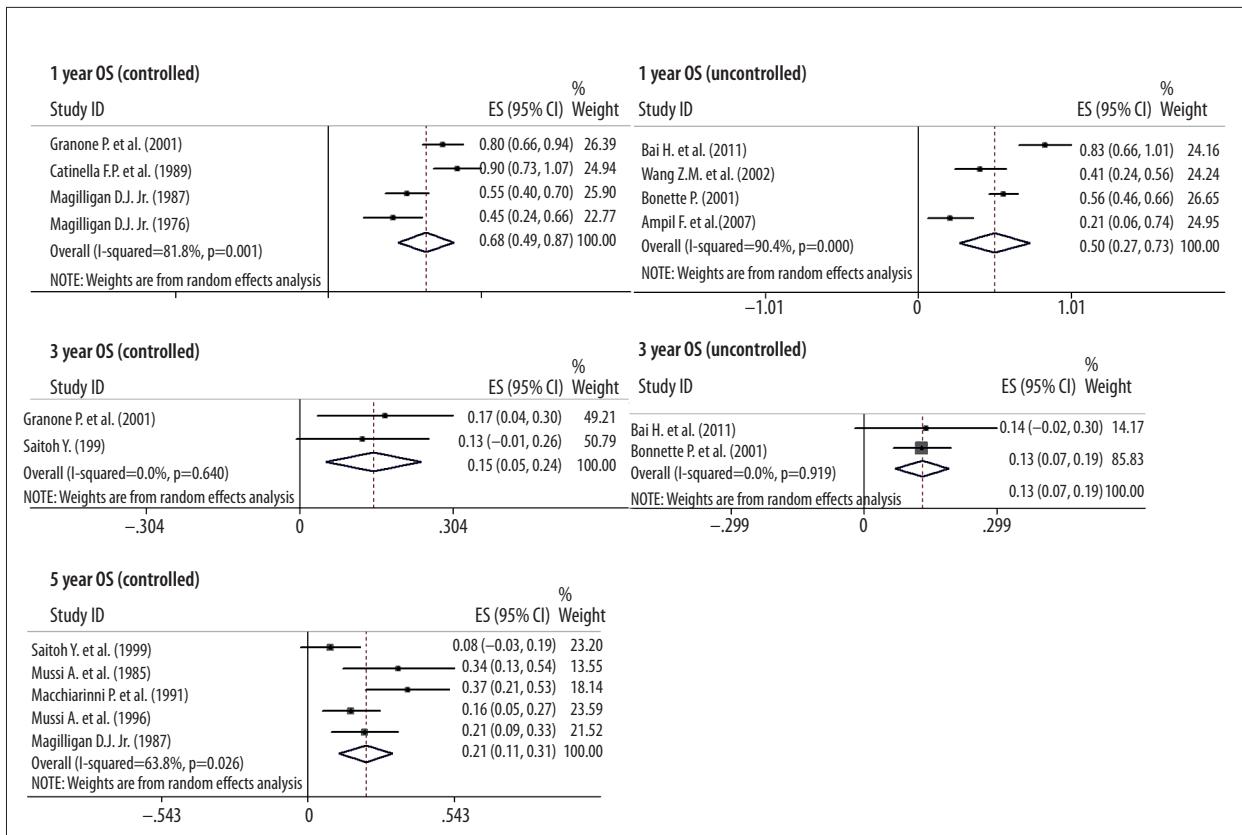


Figure 4. In the surgery group, the 1- and 3-year OS were 68% and 15% in patients with controlled primary tumors, and 50% and 13% in the other patients with uncontrolled primary tumors. The 5-year OS was up to 21% in patients with controlled primary tumors.

during the last decade [16]. SRS has become popular as a treatment option for brain metastases, especially for the SBM, due to being less invasive than surgical resection and exposing healthy tissue to less radiation than WBRT [23]. In addition, for patients with 1–2 brain metastases, SRS can achieve long-term survival as well as neurosurgery, and both SRS alone and SRS with WBRT offer equivalent levels of survival compared to patients treated with surgery followed by WBRT [25].

Which management is preferable for patients with SBM – neurosurgery or SRS? No convincing results have been found and controversy still exists. A prospective study by Muavecic et al. [24] showed that the treatment results did not differ in terms of survival (P=0.8), neurological death rates (P=0.3), and freedom from local recurrence (P=0.06) between the patients treated with SRS and those treated with surgical resection followed by WBRT. Similarly, several retrospective studies [19,24,25] also indicated that there was no survival difference between the 2 treatment groups. However, Bindal et al. [26] reported that the MST in the surgery group was significantly longer than in the SRS group (16.4 months versus 7.5 months), and that there was a higher incidence of death from neurological causes in the SRS group than in the surgery group (50%

and 19%, respectively). In our analysis, there was no statistical difference between brain surgery and SRS in patients with SBM from NSCLC. However, 71.6% and 20.5% received thoracic surgery and radiation therapy, respectively, in the surgery group and only 10.4% and 8.6% in the SRS group, so SRS as a new therapy showed a promising role in the treatment of SBM. In addition, several studies evaluated the treatment efficacy of neurosurgery combined with SRS, and demonstrated a significant improvement in survival and local tumor control in those patients.

In several retrospective studies [27,28], univariate analysis showed that survival times could be improved when both the primary lung tumor and brain metastases were resected, thus removal of the primary site and SBM appears to be an effective treatment for long-term survival. The American National Cancer Institute reported that the 5-year survival rates of patients with stage IIIA, IIIB, and IV disease were 14%, 5%, and 1%, respectively, and other studies have also reported similar 5-year survival rates for stages IIIB and IV (1–5%) [29,30]. In this study, sub-analysis of the surgery group showed that patients who received resection of both primary and metastasis lesion had a high 5-year survival rate (up to 21%), which is

significantly higher than that of stage IIIA. Therefore, we believe that patients with resectable NSCLC with SBM should be reclassified as a new stage.

There are several limitations in our systematic review. First, no randomized controlled trials were included, and most of the eligible studies were non-comparative studies with low certification strength because of the rarity of this particular NSCLC presentation. Second, there are more cases in the surgery group because surgery is more acceptable clinically, and the number of patients in each group is not well matched. Third, we failed to get the survival outcomes of the stage of intra-thoracic, because no separate outcomes were reported. Fourth, publication bias is also inevitable. Although these limitations exist, we have enough confidence to believe that there are no significant differences in MST and survival rate between the surgery group and SRS group. Furthermore, patients who received resection of both primary and metastasis had a high 5-year survival rate that challenged the present stage IV classification of resectable NSCLC with SBM. Prospective and multi-center

studies with larger sample sizes are needed to further confirm the results of our study.

Conclusions

NSCLC with brain metastases often has poor prognosis, but patients with NSCLC with SBM exhibit long-term survival. Our results show that patients with SBM from NSCLC can equally benefit from stereotactic radiosurgery and surgery. In addition, the excision of primary lung lesions and SBM is recommended for patients with resectable NSCLC combined with SBM.

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Conflict of interest

The authors declare that they have no conflict of interest.

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