Original Article

Systemic Therapy after Radiotherapy Significantly Reduces the Risk of Mortality of Patients with 1–3 Brain Metastases: A Retrospective Study of 250 Patients

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Abstract

Background: For patients with a brain metastasis (BM), systemic therapy is usually administered after the completion of radiotherapy, especially in cases of multiple BMs. However, the role of systemic therapy in patients with a limited number of BMs is not clear. Therefore, we conducted a retrospective study to explore this question.
Methods: Consecutive patients with a pathologically confirmed malignancy and 1–3 intracranial lesions that had been documented within the last decade were selected from the databases of three hospitals in China.
Results: A total of 250 patients were enrolled; of them, 135 received radiotherapy alone and 115 received radiotherapy plus systemic therapy. In patients receiving whole-brain radiation therapy (WBRT) as radiotherapy, 28 received WBRT alone and 35 patients received WBRT plus systemic therapy. Of the patients treated with stereotactic radiosurgery (SRS), 107 received SRS alone and 80 received SRS plus systemic therapy. Multivariate analysis revealed that systemic therapy significantly reduced the risk of mortality compared with radiotherapy alone (hazard ratio [*HR*] = 0.294, 95% confidence interval [*CI*] = 0.158–0.548). Further, when the analysis was conducted in subgroups of WBRT (*HR* = 0.230, 95% *CI* = 0.081–0.653) or SRS (*HR* = 0.305, 95% *CI* = 0.127–0.731), systemic therapy still showed the ability to reduce the risk of mortality in patients with BMs.
Conclusion: Systemic therapy after either SRS or WBRT radiotherapy may significantly reduce the risk of mortality of patients with 1–3 BMs.

Key words: Brain Metastasis; Stereotactic Radiosurgery; Systemic Therapy; Whole-brain Radiation Therapy

Introduction

Brain metastasis (BM) is a common complication of patients with malignant disease and its incidence continues to rise due to the improvement of therapeutic efficacy that makes long-term survival possible. Moreover, more frequent brain screening for specific malignant diseases and the efficiency of imaging have led to the diagnosis of BM at early stages.[1] BM is associated with a significant reduction in a patient's health-related quality of life, neurological/neurocognitive compromise, and life expectancy. Without treatment, the median overall survival (OS) for patients with BM is only 4–7 weeks.[2-4] Radiotherapy, including stereotactic radiosurgery (SRS) and whole-brain radiation therapy (WBRT), has been the most commonly used noninvasive technique in patients with a BM. WBRT has been a standard treatment for BMs for several decades and can prolong OS by 3–6 months.[5,6] Considering the potential long-term side effects caused by WBRT, SRS has emerged as an alternative radiotherapy in the recent years and is especially used for patients with a limited number of intracranial lesions. Although both SRS

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and WBRT have satisfactory efficacy of local control and neurological symptom alleviation, most patients with a BM die from systemic diseases other than intracranial failure. Therefore, many physicians have advocated for using systemic therapy in conjunction with radiotherapy. However, the role of systemic therapy in patients with a limited number of intracranial lesions has not been fully investigated. To further explore this question, we performed a retrospective study and enrolled 250 patients with 1–3 BMs.

Methods

Ethical approval

The study protocol was reviewed and approved by the institutional review boards and ethics committees of three hospitals (Beijing Tiantan Hospital, The Second Hospital of Dalian Medical University, Beijing Shijitan Hospital).

Inclusion/exclusion criteria

Patients who had 1–3 BMs over the last decade were selected from the databases of three hospitals in China, which are Beijing Tiantan Hospital, The Second Hospital of Dalian Medical University, Beijing Shijitan Hospital. Other inclusion criteria were as follows: (1) primary disease was confirmed by pathology; (2) no sign of secondary malignancy was documented during the follow-up; (3) a BM was documented by magnetic resonance imaging and/or computed tomography with contrast; (4) extracranial disease was evaluated at the time of BM; and (5) medical records of post-BM therapy were complete. Exclusion criteria were as follows: (1) meningeal metastasis and (2) a history of cranial radiotherapy or surgery.

Postbrain-metastasis treatment

A consultation committee includes experts from three hospitals coordinated treatment strategies. The SRS dose was prescribed in accordance with the tumor margin. Metastases with a maximum diameter of up to 2 cm were treated with doses of 22–25 Gy and those larger than 2 cm were treated with doses of 18–20 Gy. The WBRT dosage schedule was 30 Gy in 10 fractions over 2.0–2.5 weeks. After the completion of radiotherapy, Karnofsky Performance Status (KPS) and organ function were reevaluated. For patients with a KPS >60 and adequate organ function, four to six cycles of disease-specific systemic therapy were recommended routinely within 1 month. In addition, local therapies for primary tumor and/or metastases outside of the brain were allowed, especially in patients who rejected systemic therapy. At the time of tumor progression, second- or third-line systemic therapy could be delivered at the discretion of the investigators.

Follow-up

At completion of the planned therapy, a routine follow-up was conducted. The follow-up interval was every 3 months for the first 2 years and then every 6 months for the next 3 years. At each follow-up, medical history, general physical examination, complete blood count, serum chemistry, and radiographic examinations were repeated.

Statistical analysis

IBM SPSS Statistics 19.0 software (SPSS Inc., Armonk, NY, USA) was used for data analysis. Chi-square test was employed for the analysis of categoric variables. The Kaplan–Meier method was used to estimate survival. BM-free survival was calculated from the date of diagnosis to the date at which a BM was documented radiographically. Post-BM survival (PBMS) was determined from the date of the documented BM to the date of death or the last follow-up visit. The log-rank test was used to compare survival curves. Cox regression was used for multivariate analysis.

Results

Patient characteristics

A total of 250 consecutive patients with a BM were selected from the databases of three hospitals. Primary diseases were diagnosed between August 1999 and June 2015 and BMs were documented between September 2006 and June 2015. The primary malignancy was diagnosed as non-small cell lung cancer (NSCLC) in 139 patients (55.6%), small cell lung cancer in 45 patients (18.0%), breast cancer in 27 patients (10.8%), colorectal cancer in 23 patients (9.2%), and gastric cancer in 16 patients (6.4%). A total of 135 patients (54.0%) received radiotherapy alone after the occurrence of a BM, but 115 patients (46.0%) received additional systemic therapy after the completion of radiotherapy [Table 1]. The median course of systemic therapy was 3 (range: 2–8) and the median number of regimens was 1 (range: 1–3).

After statistical analysis, characteristics such as gender, smoking status, age at the time of BM, KPS, and the number of BMs were comparable between the radiotherapy group and the radiotherapy plus systemic therapy group. In terms of pathology, patients were classified as adenocarcinoma and nonadenocarcinoma, and the pathology distribution was comparable between the radiotherapy group and the combination group. Similar comparisons were also conducted in subgroups stratified according to radiotherapy technique. In patients treated with SRS, a significantly higher proportion of patients had an extracranial metastasis in the combination therapy group. In patients treated with WBRT, the proportion of patients younger than 65 years was significantly higher than that in the combination therapy group [Table 1].

Univariate analysis

The median follow-up time after the occurrence of a BM was 7 months (range: 1–52 months) in live patients. The median intracranial local control time of radiotherapy alone was 12 months and that of radiotherapy plus systemic therapy was 20 months (P = 0.021). Univariate analysis revealed that patients who received systemic therapy had a significantly longer median PBMS compared with those who received radiotherapy alone (47 months vs. 21 months, P = 0.001). In terms of radiotherapy techniques, SRS led to a significantly longer median PBMS compared with WBRT in patients receiving radiotherapy alone (22 months vs. 14 months, P = 0.016). Further, systemic therapy after SRS

Table 1: Comparison of clinical characteristics between patients receiving SRS or WBRT alone and SRS or WBRT plus systemic therapy, *n* (%)

Characteristics	SRS (*n* = 107)	SRS + S (*n* = 80)	χ^2	*P*	WBRT (*n* = 28)	WBRT + S (*n* = 35)	χ^2	*P*
Gender								
Male	58 (54.2)	47 (58.8)	0.509	0.470	13 (46.4)	24 (68.6)	10.824	0.001
Female	49 (45.8)	33 (41.2)			15 (53.6)	11 (31.4)		
Smoking status								
Never a smoker	72 (67.3)	46 (57.5)	1.959	0.160	20 (71.4)	22 (62.9)	1.447	0.220
Current smoker	35 (32.7)	34 (42.5)			8 (28.6)	13 (37.1)		
Age at the time of BM								
≤65 years	74 (69.2)	63 (78.8)	2.599	0.110	16 (57.1)	26 (74.3)	6.395	0.011
>65 years	33 (30.8)	17 (21.2)			12 (42.9)	9 (25.7)		
KPS								
>70	92 (86.0)	71 (88.7)	0.411	0.520	22 (78.6)	30 (85.7)	1.697	0.190
≤70	15 (14.0)	9 (11.3)			6 (21.4)	5 (14.3)		
Number of BMs								
1	80 (74.8)	60 (75.0)	0.001	1.000	17 (60.7)	22 (62.9)	0.085	0.770
2–3	27 (25.2)	20 (25.0)			11 (39.3)	13 (37.1)		
Presence of extracranial metastasis at the time of BM								
No	38 (35.5)	14 (17.5)	8.189	0.004	5 (17.9)	9 (25.7)	1.865	0.170
Yes	69 (64.5)	66 (82.5)			23 (82.1)	26 (74.3)		
Primary site								
Non-small cell lung cancer								
Adenocarcinoma	41 (38.4)	49 (61.2)		–	5 (17.9)	12 (34.3)		–
Squamous cell carcinoma	9 (8.4)	10 (12.5)			3 (10.7)	2 (5.7)		
Other	3 (2.8)	5 (6.3)			–	–		
Small cell lung cancer	13 (12.1)	9 (11.2)			8 (28.5)	15 (42.9)		
Breast cancer	14 (13.1)	4 (5.0)			5 (17.9)	4 (11.4)		
Colorectal cancer	14 (13.1)	1 (1.3)			6 (21.4)	2 (5.7)		
Gastric cancer	13 (12.1)	2 (2.5)			1 (3.6)	–		
Histology								
Adenocarcinoma	82 (76.6)	56 (70.0)	1.258	0.260	17 (60.7)	18 (51.4)	2.029	0.150
Nonadenocarcinoma	25 (23.4)	24 (30.0)			11 (39.3)	17 (48.6)		

–: Not applicable; BM: Brain metastasis; KPS: Karnofsky Performance Status; WBRT: Whole-brain radiation therapy; SRS: Stereotactic radiosurgery; S: Systemic therapy.

or WBRT led to a significantly longer median PBMS than SRS alone (50 months vs. 22 months, $P = 0.048$) or WBRT alone (47 months vs. 14 months, $P = 0.001$). However, the median PBMS was comparable between patients who received SRS plus systemic therapy and those who received WBRT plus systemic therapy ($P = 0.930$) [Figure 1].

Multivariate analysis

Multivariate analysis revealed that KPS and extracranial metastasis occurrence were independent factors for PBMS. Patients with a KPS <70 and an extracranial metastasis at the time of BM had a significantly higher risk of mortality. Additionally, systemic therapy was found to significantly reduce the risk of mortality compared with radiotherapy alone (hazard ratio [*HR*] = 0.294, 95% confidence interval [*CI*] = 0.158–0.548, $P < 0.001$). In terms of radiotherapy techniques, the efficacy of SRS did not show superiority to WBRT in the multivariate analysis, although SRS led to a significantly longer median PBMS compared with WBRT in the univariate analysis. To further explore the role of systemic therapy on radiotherapy, similar multivariate analyses were conducted in subgroups stratified according to radiotherapy technique. Systemic therapy following either WBRT (*HR* = 0.230, 95% *CI* = 0.081–0.653, $P = 0.006$) or SRS (*HR* = 0.305, 95% *CI* = 0.127–0.731, $P = 0.008$) significantly reduced the risk of mortality of patients with 1–3 BMs [Tables 2 and 3].

Discussion

The main finding of our study was that when analyzed by univariate or multivariate analysis, systemic therapy significantly reduced the risk of mortality of patients with 1–3 intracranial lesions compared with radiotherapy alone. Further, even in subgroups stratified according to radiotherapy technique, systemic therapy also showed a prognosis-improving ability. Given that a BM is a hematogenous dissemination and that extracranial disease is frequently present at the time of BM, radiotherapy, which acts as a local therapy, may not be adequate for systemic control of disease. Thus, many pilot studies that have mostly been conducted in NSCLC patients with multiple BM have explored the role of systemic therapy combined with

radiotherapy. WBRT was the main radiotherapy technique utilized in previous studies because it was considered the standard care for patients with a BM. The results from most single-arm studies have suggested that systemic therapy following WBRT is tolerable.[7-10] Several control studies have found that systemic therapy can improve the response rate of intracranial lesions and prolong patients' progression-free survival and even OS.[11-13] However, the results from other studies have not found that systemic therapy has clinical benefits.[14-17] Studies involving patients with a limited number of intracranial lesions are limited. The Radiation Therapy Oncology Group (RTOG) 0320 study is a randomized study to explore whether systemic therapy after radiotherapy can improve OS in NSCLC patients with 1–3 BMs. Unfortunately, the study has not yet been completed.

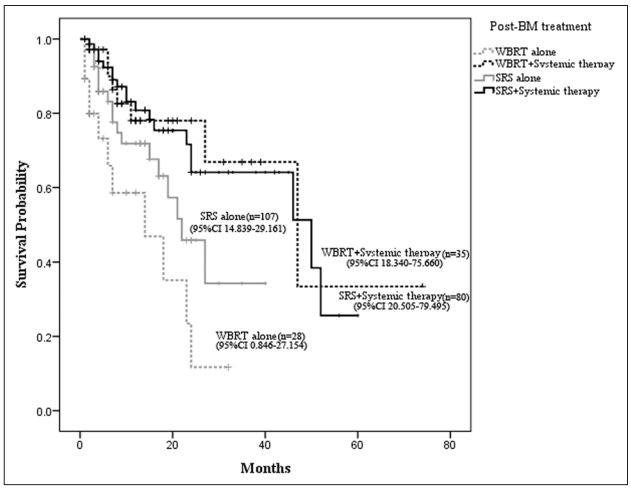

Figure 1: Postbrain metastasis survival comparison between radiotherapy alone and radiotherapy plus systemic therapy groups. BM: Brain metastasis; WBRT: Whole-brain radiation therapy; SRS: Stereotactic radiosurgery; *CI*: Confidence interval.

Reasons for such conflicting results may be complicated. First, temozolomide has been the most common agent chosen as a systemic therapy regimen because it is believed to penetrate the blood–brain barrier.[18] Moreover, its radiosensitive effect and relatively lower toxicity have made it an ideal systemic therapy regimen, especially when administered concomitantly with WBRT.[19] However, with the exception of glioma, temozolomide is not the standard systemic therapy regimen used for most solid tumors. It is possible that temozolomide may have satisfactory short-term effects, such as a higher response rate and improved local control, but may not have long-term survival benefits, which are achieved mainly by systemic control of diseases outside the brain. Tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib are other types of agent that have shown similar characteristics to temozolomide when combined with WBRT.[20-22] The only difference between temozolomide and TKIs is that TKIs

Table 2: Multivariate analysis in the WBRT subgroup

Variables	*HR*	95% *CI*	*P*
Gender (female vs. male)	1.123	0.335–3.768	0.850
Smoking status (current vs. never)	0.610	0.152–2.445	0.480
Age at the time of BM (>65 years vs. ≤65 years)	1.535	0.502–4.689	0.450
KPS (≤70 vs. >70)	3.320	1.073–10.276	0.037
Number of BMs (2–3 vs. 1)	1.228	0.419–3.602	0.710
Presence of extracranial metastasis at the time of BM (yes vs. no)	7.714	1.222–48.681	0.030
Histology (nonadenocarcinoma vs. adenocarcinoma)	0.767	0.206–2.862	0.690
RPA*	6.382	3.288–12.384	<0.001
Treatment strategy (WBRT + S vs. WBRT)	0.230	0.081–0.653	0.006

*RPA was not analyzed simultaneously with the age at the time of BM, KPS, and presence of extracranial metastasis at the time of BM. *HR*: Hazard ratio; *CI*: Confidence interval; BM: Brain metastasis; KPS: Karnofsky Performance Status; RPA: Recursive partitioning analysis; WBRT: Whole-brain radiation therapy; S: Systemic therapy.

Table 3: Multivariate analysis in the SRS subgroup

Variables	*HR*	95% *CI*	*P*
Gender (female vs. male)	0.850	0.376–1.918	0.690
Smoking status (current vs. never)	0.909	0.434–1.904	0.800
Age at the time of BM (>65 years vs. ≤65 years)	0.882	0.420–1.853	0.740
KPS (≤70 vs. >70)	9.990	4.434–22.505	<0.001
Number of BMs (2–3 vs. 1)	1.041	0.467–2.318	0.920
Presence of extracranial metastasis at the time of BM (yes vs. no)	3.956	1.418–11.037	0.009
Histology (nonadenocarcinoma vs. adenocarcinoma)	1.069	0.429–2.662	0.880
RPA*	4.924	2.015–12.034	<0.001
Treatment strategy (SRS + S vs. SRS)	0.305	0.127–0.731	0.008

*RPA was not analyzed simultaneously with the age at the time of BM, KPS, and presence of extracranial metastasis at the time of BM. *HR*: Hazard ratio; *CI*: Confidence interval; BM: Brain metastasis; KPS: Karnofsky Performance Status; RPA: Recursive partitioning analysis; SRS: Stereotactic radiosurgery; S: Systemic therapy.

show dramatic efficacy in patients with NSCLC. However, the efficacy of TKIs has shown a close correlation with *EGFR* mutation status. Only patients with mutations within exon 19 and/or 21 of *EGFR* have benefited from treatment with TKIs (even NSCLC patients with a BM).[23-25] Unfortunately, the *EGFR* mutation status has been unknown for most patients in studies exploring the efficacy of TKIs combined with WBRT.[10,13,15,17] Thus, the results are difficult to interpret, especially negative results. Furthermore, probably due to ethical concerns, the design of some studies has allowed the administration of systemic therapy in the control arm after the completion of treatment, especially in patients with extracranial metastases, which may compromise the efficacy of combination therapy.[11,12,16] Otherwise, the samples recruited in most studies have been relatively small wherein only dozens of patients have been enrolled. Even some well-designed phase II or III studies have been discontinued due to slow accrual, which has interfered with the power of statistical analyses.[16,17]

Compared with the studies by others described above, additional explanations for the positive results achieved in our study include one or more of the following: (1) patients in the current study received disease-specific systemic therapy regimens; (2) following treatment failure, due to either intracranial or extracranial progression, patients were able to receive second- or third-line systemic therapy; (3) the systemic therapy applied in our study was sequential and it was likely easier for patients to finish a planned course when compared with concomitant treatment strategies; and (4) no one received systemic therapy in the radiotherapy only group since ethical concerns could be avoided. In our study, a total of 250 patients were enrolled, of which, 135 received radiotherapy alone and 115 received radiotherapy plus systemic therapy. Multivariate analysis revealed that recursive partitioning analysis (RPA) was an independent prognostic factor. RPA is an important index that has been used for the prognostic evaluation of patients with a BM.[3,26] Based on age, KPS, and the presence of an extracranial metastasis, BM patients were classified into three prognostic groups. Although our study was retrospective in nature, patient characteristics were balanced between the treatment groups, especially those factors of RPA. Further, multivariate analysis revealed that systemic therapy could significantly reduce the risk of mortality in patients with BM.

To further explore the role of systemic therapy, analyses were conducted in subgroups stratified according to radiotherapy technique. For the WBRT subgroup, the number of patients was relatively small; 28 patients received WBRT alone while 35 received WBRT plus systemic therapy. Additionally, characteristics between the WBRT alone patients and WBRT plus systemic therapy patients were not well balanced. The proportion of patients under 65 years of age was significantly higher in the combination therapy group. However, age was not proven to be an independent prognostic factor in our cohort. After adjustment, the prognostic significance for systemic therapy remained. Based on these findings, it is warranted that systemic therapy should be considered after the completion of radiotherapy.

In terms of radiotherapy technique, data from our cohort showed that the median PBMS of SRS was significantly longer than that of WBRT in patients with 1–3 intracranial lesions; however, in the multivariate analysis, the prognosis-improving value of SRS diminished. The palliative effects of WBRT on BM have been appreciated for over 50 years. Recently, there has been more focus on the importance of focal aggressive therapy, such as SRS, which has been used alone or in combination with WBRT. RTOG 9508 was a randomized study to explore the efficacy of WBRT with or without SRS in patients with 1–3 intracranial lesions.[27] The results showed that only patients with a single unresectable BM could benefit from combination therapy. However, a randomized controlled study conducted by Aoyama *et al*. did not find survival differences between SRS and SRS plus WBRT in patients with 1–4 intracranial lesions.[28] Further, a meta-analysis of three randomized controlled trials evaluating SRS with or without WBRT in patients with 1–4 intracranial lesions also concluded that combination therapy does not have survival benefits.[29] Thus, there is no consistent evidence that WBRT plus SRS is superior to SRS alone, especially in patients with a limited number of intracranial lesions. Considering the potential long-term toxicity including cognitive deterioration and cerebellar dysfunction following WBRT, it is increasingly being omitted from initial treatment strategies. Indeed, the decline in the clinical use of WBRT underlies the low accrual of studies, as more patients have chosen SRS.

Similarly, SRS was the most common radiotherapy technique applied in our cohort. A total of 107 patients received SRS alone and 80 patients received SRS plus systemic therapy. Very few researchers have studied the role of systemic therapy when combined with SRS. As shown in our study, patient characteristics were not well balanced between the SRS and SRS plus systemic therapy groups. A significantly higher proportion of patients in the combination treatment group presented with extracranial disease at the time of BM. We attributed this to physician prevalence (systemic therapy was often reserved for those with systemic disease). Multivariate analysis revealed that the presence of extracranial disease was an independent factor that indicated an increased risk of mortality whenever analysis was conducted in the whole group or in the subgroups stratified according to radiotherapy technique. However, systemic therapy was still able to significantly reduce the risk of mortality compared with SRS alone in the multivariate analysis. Therefore, based on these results, it is reasonable to conclude that systemic therapy should be considered in patients with 1–3 intracranial lesions after the completion of SRS.

In conclusion, our study found that, in patients with 1–3 BMs, systemic therapy significantly reduced the risk of mortality in patients receiving either SRS or WBRT as radiotherapy. Future studies with a careful design are needed to investigate effective combination regimens and reasonable combination strategies.

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Conflicts of interest
There are no conflicts of interest.

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