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Brain metastasis reirradiation in patients with advanced breast cancer

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ABSTRACT

The outcome of recurrent brain metastasis is dismal. This study aims to assess the clinical outcomes and toxicity of reirradiation as a salvage treatment for progressive brain metastasis in patients with advanced breast cancer. Between July 2005 and September 2014, the medical records of 56 patients with brain metastasis from breast cancer were retrospectively reviewed. Of these patients, 39 received whole-brain radiotherapy (WBRT) followed by stereotactic radiosurgery (SRS) reirradiation (Group 1), and 17 received SRS followed by WBRT reirradiation (Group 2). Overall survival (OS) and brain progression-free survival rates/times were calculated using the Kaplan–Meier method. Prognostic factors were evaluated using the Cox proportional hazards model. Change in neurologic function was also assessed. The median OS was 10.8 months (range, 1.3–56.8 months). In Group 1, the median PFS time (PFS-1) was 6.5 months and the OS time was 11.4 months. Multivariate analysis revealed that longer OS was significantly associated with a high Karnofsky performance score (KPS) ($P = 0.004$), controlled extracranial metastasis ($P = 0.001$) and a good response to reirradiation ($P = 0.034$). In Group 2, the median PFS time (PFS-2) after reirradiation was 8.5 months and the OS time was 10.8 months. Multivariate analysis revealed that longer OS was significantly associated with a high KPS ($P = 0.018$). The majority of the patients had improved or stable neurological function. Reirradiation is an effective and a safe treatment for patients with brain metastases from breast cancer. It might delay the progression of intracranial disease and improve neurological function. A suitable patient selection for reirradiation was suggested.

KEYWORDS: brain metastasis, reirradiation, breast cancer, survival, prognosis

INTRODUCTION

Breast cancer is the most common malignancy in women worldwide [1]. For women with breast cancer, the principle cause of death is not the primary tumor, but its distant metastasis. Throughout its disease course, ~10–15% of breast cancer patients will develop symptomatic brain metastasis, and ~30% of breast cancer patients will have brain disease at autopsy [2].

Radiotherapy is the most common local treatment for most patients with extensive brain disease. Despite the use of whole-brain radiotherapy (WBRT) with the addition of a local therapy such as stereotactic radiosurgery (SRS) or surgical resection, recurrences continue to occur locally and elsewhere in the brain, which require further therapeutic intervention. Treatment options for recurrent brain metastatic disease include repeat WBRT, SRS, surgery and chemotherapy [3]. However, there is a lack of Class I or II evident definitive treatment recommendations [4]. The choice for reirradiation treatment has been mainly based on the previous treatment modalities, the number of brain metastases, and life expectancy. Generally, patients who have received WBRT in initial radiotherapy have been treated with SRS as the preferred modality for reirradiation therapy. Because of ongoing concerns over side effects on neurocognitive function and quality of life associated with the addition of WBRT, as well as its lack of a survival benefit [5, 6], treating physicians have tended to choose SRS alone for patients with limited tumor lesions in the initial treatment. This strategy is associated with a significantly increased risk of distant brain failure and requires

close surveillance. Although some of the distant brain recurrence lesions can be treated by SRS again [7], WBRT is used as an effective salvage therapy for patients with multiple or large-volume brain metastases. Several studies have described the results of brain metastasis reirradiation [8–10], but these findings have differed. Most of these studies did not report the neurological function, and the relative roles of SRS and WBRT in the treatment of brain metastases remain undefined. In addition, few studies have specifically focused on breast cancer, and the reported data is limited.

In this study, we aimed to assess the clinical outcomes, neurological function change and toxicity of reirradiation as a salvage treatment for progressive brain metastasis in patients with advanced breast cancer.

MATERIALS AND METHODS

Patients and study design

The breast cancer database at our hospital was used to conduct this retrospective study. This database includes information on all patients who have received radiation of brain metastases in the institution from May 2005 to December 2014. The following data were collected from the original medical records: age, gender, date of diagnosis of brain metastasis, date when reirradiation was performed, initial tumor stage of breast cancer, tumor molecular subgroup, Karnofsky performance score (KPS), the number of brain metastases, total tumor volume, extracranial disease, radiation dose delivered, and follow-up imaging. Patients with metastatic breast cancer treated with more than one course of brain metastasis irradiation were identified, and the clinical outcomes and toxicity of reirradiation in these patients were investigated. This retrospective study was approved by the local Institutional Review Board. All patients provided written informed consent to have their medical records used for research purposes.

Radiotherapy techniques

WBRT was administered with a linear accelerator (Varian23EX), and SRS was performed by Gamma Knife (LUNATM-260) or CyberKnife (Accuray, USA). During SRS procedures, a stereotactic head frame was applied under local anesthesia. Then, patients received a computed tomography (CT) and magnetic resonance imaging (MRI) scan for treatment planning. The linear quadratic (L-Q) model was used to calculate the biological effective dose (BED) according to the following relationship: $BED = nd\ (1 + d/[\alpha/\beta])$, where d = fraction dose, n = number of fractions, $nd = D$ = total physical dose, and α/β = tissue repair capacity. An α/β value of 10 Gy for tumor effects and an α/β value of 2 Gy for normal brain tissue were assumed.

Evaluation of efficacy and side effects

Evaluation of efficacy was carried out according to the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 standards [11]. Symptoms of brain metastases were evaluated according to the neurologic function score (NFS):[12] score 0, no neurologic symptoms; score 1, minor neurologic symptoms; score 2, moderate neurologic symptoms, fully active; score 3, moderate to severe neurologic symptoms, less than fully active; and score 4, severe neurologic symptoms, inactive. Acute and chronic toxicities were assessed according to the Radiation Therapy Oncology Group (RTOG) morbidity scoring criteria [12].

Statistical analysis

Overall survival (OS) was defined as the period from time of reirradiation to the time of death or last follow-up. The progression-free survival (PFS) time was defined as the time from start of reirradiation treatment to the time of first recurrence of the primary treated site or development of new brain metastasis. Date of death was obtained from medical records. When this was not available, date of death was obtained through telephone follow-up. The final data analyses were based on information received until 15 May 2016.

Statistical tests were performed using SPSS (version 18.0, Chicago, IL, USA). Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Factors showing significance in univariate analyses were incorporated into the Cox proportional hazards method. The Cox method with backward stepwise selection was used to analyze the effects of potential independent predictors on survival. A P-value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 382 patients with metastatic breast cancer and brain metastases were found in the database from May 2005 to December 2014. Among them, 64 patients had more than one course of brain radiation. Eight patients who underwent SRS for the first and second course of radiation were excluded. Finally, 56 patients with metastatic breast cancer who had received reirradiation for brain metastasis were identified.

Patient characteristics, tumors and treatments are shown in Table 1. The patients were divided into two subgroups. The first group (Group 1) consisted of 39 patients who received WBRT as an initial treatment and were treated with SRS as reirradiation treatment; the second group (Group 2) contained 17 patients who were treated with SRS as an initial treatment and received WBRT as reirradiation treatment. In the total 56 patients, the median age at the beginning of reirradiation was 48.5 years, the median number of brain metastases was 4 (range, 1–40), and the median total tumor volume was 4.1 cm^3 (range, 0.18–65.6 cm^3). Fifty-three (94.6%) patients had extracranial disease, and 30 (53.6%) patients had HER2-positive disease. The median KPS score was 80 (range, 50–90), and the median $BED_{reirradiation}$ ($\alpha/\beta = 10$) was 44.4 Gy (range, 23.7–52.8 Gy). After reirradiation treatment, 13 (23.2%) patients received a third course of radiation with SRS, and one patient received further surgery. The median follow-up time was 10.1 months.

Treatment

In Group 1, the median dose of WBRT performed as initial irradiation was 40 Gy (range, 30–50 Gy) delivered in 20 fractions (range, 10–25), and the median dose of SRS performed as reirradiation was 17 Gy (range, 12–25 Gy) delivered in one fraction (range, 1–5). In Group 2, the median dose of SRS performed as initial irradiation was 17 Gy (range, 14–21 Gy) delivered in one fraction (range,

Table 1. Patient characteristics, tumors and treatments

Characteristics	Number of patients (%)	Group 1 (WBRT + SRS)	Group 2 (SRS + WBRT)
Total	56	39	17
Age (years)			
<50	30 (53.3)	20 (51.3)	10 (58.8)
≥50	26 (46.4)	19 (48.7)	7 (41.2)
Biologic subtype			
Luminal A	21 (37.5)	12 (30.8)	9 (52.9)
Luminal B	15 (26.8)	11 (28.2)	4 (23.5)
HER-2 positive	15 (26.8)	11 (28.2)	4 (23.5)
Triple negative	5 (8.9)	5 (12.8)	
Extracranial metastasis			
Controlled	30 (53.6)	20 (51.3)	10 (58.8)
Uncontrolled	26 (46.4)	19 (48.7)	7 (41.2)
Time interval between two courses of radiation (months)			
Median	10.5	11.1	9.1
Range	1.9–42.4	2.5–42.4	1.9–21.1
Number of brain metastases			
Median	4	3	4
Range	1–40	1–20	1–40
KPS			
<80	21 (37.5)	14 (35.9)	7 (41.2)
≥80	35 (62.5)	25 (64.1)	10 (58.8)
Response to reirradiation			
Complete remission	1 (1.8)	1 (2.6)	
Partial remission	18 (32.1)	11 (28.2)	7 (41.2)
Stable disease	33 (58.9)	24 (61.5)	9 (52.9)
Progression of disease	4 (7.2)	3 (7.7)	1 (5.9)
Treatments after reirradiation			
Chemotherapy	42 (75.0)	32 (82.1)	10 (58.8)
Anti-HER2 therapy	19 (33.9)	17 (43.6)	2 (11.8)
Hormonal therapy	32 (57.1)	18 (46.2)	14 (82.4)

PFS = progression-free survival, luminal A = ER/PR-positive and HER2-negative, luminal B = ER/PR-positive and HER2-positive, HER2 = ER/PR-negative and HER2-positive, triple-negative = ER/PR-negative and HER2-negative.

1–3), and the median dose of WBRT performed as reirradiation was 40 Gy (range, 26–44 Gy) delivered in 20 fractions (range, 13–22).

Progression-free survival

For all 56 patients, the median PFS after reirradiation was 6.7 months (range, 0.0–15.7 months). The PFS rate at 6 and 12 months was 65.7% and 13.9%, respectively. The median PFS was 6.5 and 8.5 months for Group 1 and Group 2, respectively. The 6 and 12 months PFS rates were 63.5% and 4.5%, and 61.8% and 22.1% for Group 1 and Group 2, respectively ($P = 0.039$). Multivariate analysis revealed that KPS was a factor significantly associated with the PFS of Group 1 and Group 2 [hazard ratio (HR) = 0.17, $P < 0.001$; HR = 0.071, $P = 0.019$].

In Group 1, complete information regarding intracranial failure after reirradiation was available in 64.1% (25/39) of the patients. Of these, 20% of recurrences had in-field-only recurrences (5/25), 56% had out-field-only recurrences (14/25), and 24% had simultaneous in-field and out-field recurrences (6/25).

Overall survival

The median follow-up time was 10.1 months. For the 56 patients, the median OS after reirradiation was 10.8 months (range, 1.3–56.8) (Fig. 1). The OS rates at 6 and 12 months were 76.8% and 43.4%, respectively. The median OS from the initial diagnosis of brain metastasis was 23.8 months (range, 5.7–85.4 months). At the time of last follow-up, 48 (85.7%) patients had died. Of these, 18 (37.5%) patients had died of brain metastasis and 30 (62.5%) patients of active extracranial disease. The median overall survival after reirradiation was 11.4 and 10.8 months for Group 1 and Group 2, respectively. The 6 and 12 months OS rates were 74.4% and 40.3%, and 70.1% and 38.2% for Group 1 and Group 2, respectively ($P = 0.948$). Furthermore, in Group 1 multivariate analysis revealed that OS was significantly associated with KPS, extracranial metastasis, and response to reirradiation (Table 2). The median OS time was 15.1 months in patients with a high KPS (≥80) and 4.6 months in patients with a low KPS [<80; HR, 0.31; 95% confidence interval (CI), 0.14–0.69; $P = 0.004$]. The median OS time was 9.2 months in patients with uncontrolled extracranial metastasis and 11.6 months in patients with controlled extracranial metastasis (HR, 2.36; 95% CI, 1.06–5.23; $P = 0.001$). The median OS time was 16.0 months in patients who had complete remission and partial remission, while the median OS time was 8.1 months in patients who had stable or progression of disease (HR, 1.91; 95% CI, 1.28–2.84; $P = 0.034$). Univariate analysis revealed that OS was associated with the KPS score, extracranial metastasis and response to reirradiation. Other examined variables (such as age, tumor molecular subgroup, the number of brain metastases, total tumor volume, radiation dose, and interval time between two courses) were not associated with survival.

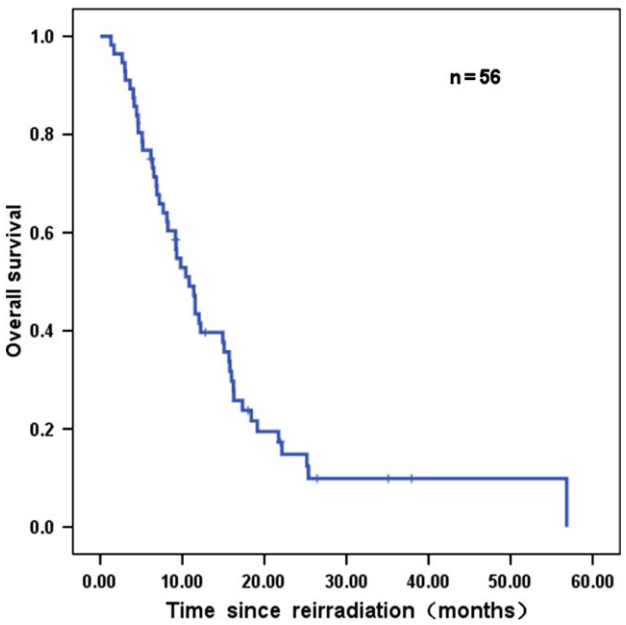

Fig. 1. Overall survival since reirradiation. The Kaplan–Meier curve for the overall survival of 56 patients is shown.

Effects on neurological function and toxicity

Neurological function was evaluated according to NFS [12]. NFS changes are shown in Table 3. On the basis of NFS, of the 56 patients, 24 (42.9%) patients had improved neurological function, 27 (48.2%) patients had stable neurological function, 3 (5.4%) patients had worsened neurological function and 2 (3.6%) patients were not evaluable. Of the 3 patients who had worsened symptoms, one had tumor progression during reirradiation, one had expanded peritumoral edema that caused limb movement obstacles, and one had cystic brain metastases.

Acute radiation-related toxicity of the central nervous system after reirradation was assessed. The majority of the patients had low-grade toxicity on the basis of the RTOG criteria [12], including 18 (32.2%) patients who had Grade 0 toxicity (no change over baseline), 20 (35.7%) patients who had Grade 1 toxicity, 13 (23.2%) patients who had Grade 2 toxicity, 4 (7.1%) patients who had Grade 3 toxicity, and one patient was not evaluable. None of

Table 2. Multivariable analysis estimating the prognostic factors for survival

Factors	Hazard ratio (95% CI)	*P* value
Group 1		
KPS (≥80 vs <80)	0.31 (0.14–0.69)	0.004
Extracranial metastasis (Uncontrolled vs Controlled)	2.36 (1.06–5.23)	0.001
Response after reirradiation (SD + PD vs CR + PR)	1.91 (1.28–2.84)	0.034
Group 2		
KPS (≥80 vs <80)	0.134 (0.12–0.71)	0.018

CI = confidence interval, KPS = Karnofsky performance score, CR = complete remission, PR = partial remission, SD = stable disease, PD = progression of disease.

Table 3. Change in neurologic function score

Neurologic function score	Patient no. (%) before reirradiation	Patient no. (%) after reirradiation
0	12 (22.2)	14 (25.9)
1	7 (13.0)	21 (38.9)
2	15 (27.8)	8 (14.8)
3	17 (31.5)	8 (14.8)
4	3 (5.6)	3 (5.6)
Unable to value	2	2

Table 4. Acute radiation-related toxicities

Acute toxicities/ symptoms	Total no. (%)	Group 1 no. (%)	Group 2 no. (%)
Headache/dizziness	35 (63.6)	24 (63.1)	11 (64.7)
Nausea/vomiting	5 (9.1)	3 (7.8)	2 (11.7)
Ataxia	2 (3.6)	1 (2.6)	1 (5.8)
Dysphagia	1 (1.8)	1 (2.6)	
Seizures	1 (1.8)	1 (2.6)	
Asymptomatic	18 (32.7)	12 (31.5)	6 (35.3)

the patients had Grade 4 toxicity (severe toxicity). The details of the acute radiation-related toxicities are shown in Table 4.

DISCUSSION

With advances in modern systemic therapy, an increasing number of patients are experiencing recurrent brain progression events, and further treatments are being considered. In the present study, we retrospectively assessed the survival outcomes, neurological function change and toxicity of brain metastasis reirradiation in patients with metastatic breast cancer.

Our results showed that the median OS was 10.8 months after reirradiation in this study cohort, which is consistent with previously reported results of 9.8–19.0 months [10, 13–15]. In this study, the OS in one patient reached 85.4 months after brain metastasis and 56.8 months after SRS reirradiation. At the time of last follow-up, 48 (85.7%) patients had died. Of these patients, 30 (62.5%) patients had died of active extracranial disease. The intracranial PFS time for patients who had died of extracranial disease was longer than patients who had died of intracranial disease (7.7 vs 4.6 months, $P = 0.009$), suggesting that intracranial death might be prevented or delayed by reirradiation. In addition, in more than half of the patients who died, death was a result of extracranial disease, indicating that systemic therapy should also be strengthened. To our knowledge, five studies have analyzed or subgroup analyzed the use of SRS as reirradiation treatment in patients with brain metastases from breast cancer (Table 5). Kelly *et al.* [15] described their results using SRS as reirradiation after progression of initial treatment in a group of 79 patients from breast cancer. Of their 79 patients, 76 of whom (96%) received prior WBRT. The median OS was 9.8 months. Being HER2-positive and having stable extracranial disease were found to be associated with a favorable prognostic. Kased *et al.* [10] reported the results of reirradiarrion of a subgroup in their study. The OS after SRS was 11.7 months for 81 patients with recurrent brain metastases from breast cancer. Longer survival was associated with age <50 years, KPS of ≥70, longer interval between primary diagnosis and reirradiation, and smaller tumor volume. In our study, for the patients who received SRS as reirradiation treatment, multivariate analysis revealed that increased OS was significantly associated with high KPS and controlled extracranial metastasis, which is consistent with previous reports [15–18]. Moreover, we found that OS was significantly affected by response to reirradiation, which has not been reported in previous studies. Interestingly, one report has shown that PFS was associated with response to reirradiation [8]. These findings suggest that response to reirradiation is a prognostic factor for survival. However, the patient number was small, and the results need to be verified with a larger patient number.

Although the most useful indication for reirradiation remains unknown, it is generally accepted that patients may benefit from reirradiation under certain conditions, such as a younger age, a high KPS score, a long interval between initial therapy and reirradiation, stable extracranial lesions, smaller tumor volume, positive response to reirradiation, and a higher radiation dose [9, 16, 19]. Intracranial failure mode after reirradiation was analyzed in Group 1. The in-field failure rate was 44% (11/25), which is relatively higher than that of previous studies [15]. The higher in-field progression found in our study was probably due to the dose being administered to patients in this study being lower than the dose recommended by the RTOG 90-05 study [12]. Alternatively, it may be have been due to radionecrosis. It was difficult to distinguish progression from radionecrosis in our study because of lack of further examination.

Treatment for recurrent brain metastasis is an important concern for clinicians. The factors determining whether SRS or WBRT should be used have yet to be clarified. At present, the choice of treatment for recurrent brain metastasis depends on multiple factors, including previous treatment modalities, the number, location and size of brain metastases, and life expectancy. In the present study, the treatment options selected for progressive brain lesions were mainly based on the approaches used in initial treatment and the number of brain metastases. The 39 patients who received WBRT in the initial radiotherapy received SRS in the second course of radiation, and the 17 patients who received SRS in the initial radiotherapy received WBRT in the second course of radiation. Growing evidence suggests that SRS is a reasonable treatment option for relapsing brain metastasis, and that the RTOG 90-05 protocol has already established the maximum tolerated dosage of SRS in reirradiation after a course of WBRT [8, 12, 20]. Data on salvage WBRT after initial SRS are limited. Concerning the risks of subacute leukoencephalopathy and neurocognitive dysfunction associated with WBRT, many clinicians tend to delay the use of WBRT [6, 21]. But WBRT can reduce the rate of distant brain recurrence [22, 23] and is still the standard treatment for patients with multiple

Table 5. Results of reirradiation for patients with brain metastases from breast cancer (previous studies)

Authors (years)	Treatment (n)	Previoustreatment	PFS for reirradiation	MST (m)	Prognostic factors
Combs (2004) [13]	SRS ($n = 39$)	WBRT	At original sites: 9 months	19	Age < 40
			At distant brain sites: 7 months		
Akyurek (2007) [14]	SRS ($n = 15$)	WBRT	At original site, 1-year local control rate: 77%;	14	KPS ≥ 90, SIR ≥ 6, ER-positive, post-menopausal status
			At distant brain sites, 1-year distant control rate: 57%		
Kased (2009) [10]	SRS ($n = 81$)	WBRT ($n = 77$)	Overall in brain: 6.2 months	11.7	Age < 50 years; KPS ≥ 70, Longer interval from primary diagnosis, smaller volume
		Surgery ($n = 4$)	Overall in brain, 1-year control rate: 16%		
Kelly (2012) [15]	SRS ($n = 79$)	WBRT	Overall in brain: 5.7 months	9.8	HER2-positive, stable extracranial disease
Present study	SRS ($n = 39$)	WBRT	Overall in brain: 6.5 months	11.4	KPS ≥ 80, Controlled extracranial metastasis, tumor response to reirradiation
			Overall in brain, 6 and 12 months PFS rate: 63.5% and 4.5%, respectively		
	WBRT ($n = 17$)	SRS	Overall in brain: 8.5 months	10.8	KPS ≥ 80,
			Overall in brain, 6 and 12 months PFS rate: 61.8% and 22.1%, respectively		

PFS = progression-free survival, MST = median survival time, ER = estrogen receptor, KPS = Karnofsky performance score, SIR = score index for radiosurgery.

brain metastases. Aoyama *et al.* [22] carried out a randomized controlled trial to investigate the role of WBRT in patients with one to four solid brain metastases. Patients were randomly assigned to receive WBRT plus SRS (65 patients) or SRS alone (67 patients). The 12-month actuarial rate of developing a distant brain metastases was significantly higher in the SRS-only group than the WBRT + SRS group (63.7 vs 41.5%, $P = 0.003$). In the present study, the median PFS was 8.5 months for patients who received WBRT as reirradiation, and 6.5 months for patients who received SRS as reirradiation ($P = 0.039$). These data suggest that WBRT can reduce intracranial relapse, particularly distant brain metastasis. For progressive brain metastasis, WBRT may be considered as a salvage therapy when metastasis is disseminated recurrence and not amenable to SRS. However, considering the side effects, the use of WBRT has been limited to one course in our institution.

This study indicated that the majority of patients had improved or stable neurological function with low-grade toxicity after reirradiation. One important aim of reirradiation is to reduce symptoms and preserve neurological function. Although 24 (42.9%) patients had improved neurological function and 27 (48.2%) patients had stable neurological function, three (5.4%) patients were observed to have worsened neurological function, including one patient who had obvious peritumoral edema before reirradiation, one patient who had cystic brain metastases, and one patient who had tumor progression during reirradiation. This observation indicates that caution should be given in performing reirradiation when patients have peritumoral edema or cystic brain metastases. Regarding toxicity, although the majority of patients in this study had acute radiation-related side effects, all patients had Grade 0–3 toxicities, and none of them suffered from severe neurotoxicity (Grade 4) or died due to reirradiation (Grade 5). Of the 56 patients, 4 patients had Grade 3 toxicity, and 3 of these had low KPS scores (≤60). These patients may represent a subset of patients who have a declining performance status and are not suitable for receiving brain metastasis reirradiation. The main reasons why patients in this study did not have severe side effects may include the smaller lesions and lower radiation doses.

Our study had limitations that merit comments. First, our data were limited by the retrospective nature of the study. Second, it is challenging to study this population of patients because they are at their end of life and many patients die at home, and because medical record data on neurological status after treatment is limited, including late effects such as memory loss and dementia. This may result in the underreporting of treatment toxicity. However, as other investigators have pointed out, concerns about unreported late effects should be balanced by awareness of the more likely occurrence of neurological deterioration when brain metastases remains untreated [16].

In conclusion, our study revealed that reirradiation is an effective treatment for patients with brain metastases from breast cancer. It might delay the progression of intracranial disease and improve neurological function. Patients with a high KPS score, stable extracranial metastasis and good response to reirradiation might be benefit from reirradiation, whereas patients with peritumoral edema, cystic brain metastasis and a low KPS score might not be appropriate candidates for reirradiation.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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