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Effects of whole-brain radiotherapy, stereotactic ablation radiotherapy, and combined radiotherapy on brain metastases

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► ***Original article***

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ABSTRACT

***Background*:** To investigate the effects of different radiotherapy regimens on the prognosis of patients with brain metastases. ***Materials and Methods*:** Patients with brain metastases undergoing radiotherapy from January 2016 to December 2020 were retrospectively analyzed. The patients were divided into a whole-brain radiotherapy (WBRT) group, stereotactic ablative radiotherapy (SABR) group, and WBRT+SABR group, and overall survival (OS) and progression-free survival (PFS) were analyzed. ***Results*:** Forty patients were candidates for the analysis, with a median age of 57.5 years and a median follow-up time of 27.4 months. The median OS and PFS were 35.7 and 13.5 months, respectively, and the median radiotherapy dose was 41.7 Gy. The median OS times for patients who received WBRT (n = 12), SABR (n = 21), and WBRT+SABR (n = 7) were 41.8, 70.6, and 56.8 months, respectively (p = 0.7). The median PFS times were 10.2 months, 34.3 months, and 25.9 months, respectively (p = 0.322). Subgroup analysis indicated that the OS times were 25.4 months after WBRT (n = 7), 79.1 months after SABR (n = 11), and 65.9 months after WBRT+SABR (n = 5) among patients with brain metastases from lung cancer (p = 0.028). The patients had PFS times of 7.1, 33.4, and 29.1 months after irradiation with WBRT, SABR, and combination therapy, respectively (p = 0.009). ***Conclusion*:** The three different radiotherapy regimens had no significant effects on the prognosis of patients with brain metastases. SBAR was superior to WBRT and WBRT+SABR with respect to the prognosis of patients with brain metastases from lung cancer. The sample size of this retrospective study was small; therefore, larger, prospective studies are needed.

INTRODUCTION

Brain metastases are the most common intracranial tumors in adults. More than 50% of intracranial tumors are metastatic brain tumors [1, 2]. Primary tumors including lung cancer, breast cancer, kidney cancer, colorectal cancer, and melanoma cause brain metastases [2, 3]. Brain metastases are treated in a nonprimary-tumor-specific manner, and whole-brain radiotherapy (WBRT) is considered a classic treatment method. Surgical resection has been applied for large and isolated lesions, whereas stereotactic ablative radiotherapy (SABR), including stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SBRT), has been recommended for small lesions that cannot be treated surgically [4]. Previously, the median overall survival (OS) for patients with brain metastasis was approximately 4-6 months; however, the prognosis of patients with brain metastases has significantly improved with the emergence of new systematic agents, resulting in intracranial metastatic neoplasm no longer being regarded as the disease endpoint [4]. Accordingly, the therapeutic landscape is constantly being updated. As described above, WBRT, which remains the standard treatment for brain metastases, improves neurological deficits and prevents further deterioration of nerve function by controlling intracranial lesions as much as possible [3, 5]. WBRT at 30 Gy in 10 fractions has become the most conventional scheme. An OS of 4-6 months precludes observation of delayed neurological injury [4]. At present, systemic therapies based on tumor and gene subtypes are expected to become available soon, reflecting the possibility of controlling systemic and intracranial diseases, and OS for various patient subsets may be 12-18 months or even longer [4, 6].

On the other hand, with longer OS, drug resistance and other disadvantageous events may occur during treatment, and several patients may develop new intracranial foci. Reirradiation is difficult to apply due to potential aggravation of damage from previous

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WBRT. Moreover, WBRT was believed to decrease the risk of intracranial disease progression but found to have no impact on OS [7]. The above factors suggest that WBRT might not be the optimal treatment method for brain metastases. Fortunately, benefiting from equipment and technological advances, SABR, which has physical and biological advantages, has significantly improved OS, progression-free survival (PFS), and local control (LC) by shortening the course of treatment and enabling patients to receive new systemic treatment as soon as possible [8, 9]. An analysis showed that SABR improved the OS, PFS, and local control rate (LCR) of breast cancer patients with brain metastasis [10–12].

In addition, patients with more than 10 intracranial lesions were not suitable for SBAR, an irradiation dose of 30 Gy was not sufficient to eliminate all lesions, especially larger neoplasms [13], and WBRT combined with SABR was selected as an alternative approach. However, SABR plus WBRT inevitably increases neurological damage and compromises quality of life. Therefore, the radiotherapy modality that best improves the prognosis of patients requires further investigation [14, 15]. This study simultaneously compared OS and PFS among patients with brain metastases treated with WBRT, SABR, and WBRT plus SABR.

MATERIALS AND METHODS

This study retrospectively analyzed patients with brain metastases undergoing radiotherapy between January 2016 and December 2020. Inclusion criteria: age ≥ 18 years; signed informed consent; Karnofsky performance scale (KPS) ≥ 70; life expectancy ≥ 6 months; clear pathology of the primary disease; and a confirmed diagnosis of brain metastases by imaging. Exclusion criteria: severe comorbidities, such as uncontrolled severe infection, bone marrow suppression, coagulation disorders, active bleeding, cardiovascular and cerebrovascular diseases, and persistent or intractable epilepsy; severe abnormal liver or kidney function; pregnancy or lactation; and brain metastases combined with other organ metastases or new intracranial lesions after radiotherapy.

Radiotherapy procedure

A head stereotactic mask (Klarity, China) or U-shaped mask (Klarity, China) was used. Positioning was performed by computed tomography (CT) simulation (General election, GE, Discovery CT590RT, USA). The slice thickness for nonenhanced + enhanced scanning was 2.5 mm. The CT/magnetic resonance images (MRI) were fused to delineate the target volume. The gross tumor volume (GTV) was the visible tumor in the image, and a GTV margin of 2-3 mm was the planning target volume (PTV). For the WBRT target volume, the clinical target volume (CTV) was the whole brain tissue, and the CTV plus 3 mm included the PTV. The descriptive doses were as follows: WBRT: 25-30 Gy in 10 fractions (30 Gy/10 F) or 36-40 Gy/18-20 F; SABR: 36 Gy/3 F for limited brain metastases (≤ 3 foci) and 45-48 Gy/5-6 F for multiple brain metastases (4-10 lesions); and WBRT+SABR: 25-30 Gy/10 F for WBRT, a sequenced boost with 20-24 Gy/2-3 F, and a single dose ≤ 6 Gy for brainstem metastases. All organs at risk (OARs) within the scan range were delineated at 3 mm from the spinal cord and brainstem to generate the planning organ-at-risk volume (PRV). OAR dose limitation refers to the British expert consensus and recommendations from Robert D. Timmerman [12, 13]. Planning evaluation: the ≥ 98% dose line covered the target volume, the 50% dose line was < 8 mm, the 30% dose line was evaluated, and the OAR dose distribution was also evaluated. A linear accelerator (Varian TrueBeam 2691, America) and treatment planning system (Eclipse, V13.6, America) were used. Cone-beam CT (CBCT) image-guided radiotherapy (IGRT) was performed. Other treatments included steroids and 20% mannitol for brain dehydration to lower intracranial pressure.

The first follow-up was performed 2-4 weeks after radiotherapy, and then a follow-up was conducted every 3 months. Efficacy and side effects were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and the Radiation Therapy Oncology Group (RTOG) side effect evaluation criteria. PFS was the time from the start of treatment to the absence of new brain metastases and recurrences. OS was the time from the start of treatment to the end of the follow-up. This study was approved by the Ethics Committee of Hainan Cancer Hospital (2020, No. 10).

Statistical analysis

Statistical analysis was performed with SPSS 26.0. A survival table and the Kaplan–Meier method were used for survival curve analysis. $p < 0.05$ was considered statistically significant.

RESULTS

General clinical-pathological characteristics of the patients

Among 498 patients with brain metastases, approximately 72% (357/498) had lung cancer. A total of 40 patients with brain metastases undergoing radiotherapy were included in the analysis, including 19 males and 21 females, with a median age of 57.5 years (95% confidence interval (CI): 54.4-60.1 years) and a median follow-up time of 27.4 months (95% CI: 27.5-43.5 months). Twenty-three metastases originated from lung cancer (11 from lung adenocarcinoma, 10 from lung cancers with unclear

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pathological types, and two from other lung cancers, such as small-cell carcinoma and squamous cell carcinoma), five originated from breast cancer, two originated from cervical cancer, two originated from renal cancer, two originated from rectal cancer, three were first diagnosed as brain metastases, one originated from squamous cell carcinoma of the skin, one originated from tonsil carcinoma, and one originated from bladder cancer.

Survival analysis of patients with brain metastases after radiotherapy

The survival analysis of the above 40 patients with brain metastases after radiotherapy showed that the median OS of the patients was 35.7 months, as shown in figure 1a, and the median PFS was 13.5 months, as shown in figure 1b. The median time between the diagnosis of a malignant tumor and the initial diagnosis of brain metastasis was 22.3 months. The median radiotherapy dose was 41.7 Gy (18-67.5 Gy), and the median biological equivalent dose (BED, $\alpha/\beta = 10$) was 64.2 Gy (36-102 Gy). The median PFS times of the male and female patients were 20.9 months and 35.6 months, respectively, with no significant difference ($p = 0.191$). Of the 40 patients, 12 were in the WBRT group, 21 were in the SABR group, and seven were in the WBRT+SABR group. The median OS times were 41.8 months, 70.6 months, and 56.8 months, respectively (p = 0.7) (figure 2a), while the median PFS times were 10.2 months, 34.3 months, and 25.9 months, respectively (p = 0.322) (figure 2b).

Prognostic analysis of patients with brain metastases from lung cancer after radiotherapy

The above results suggested that SABR might have potential survival benefits. After considering the small sample size, the impact of the heterogeneity of the primary tumor site, pathological type, and molecular classification on the survival of the patients, subgroup analysis of the patients with brain metastases from lung cancer was conducted, with seven patients in the WBRT group, 11 patients in the SABR group, and five patients in the WBRT+SABR group. The median OS times were 25.4 months, 79.1 months, and 65.9 months, respectively ($p = 0.028$) (figure 3a), while the median PFS times were 7.1 months, 33.4 months, and 29.1 months, respectively ($p = 0.009$) (figure 3b). Subgroup analysis suggested that SABR provided a survival benefit for patients with brain metastases from lung cancer. Serious delayed side effects were not observed for all patients.

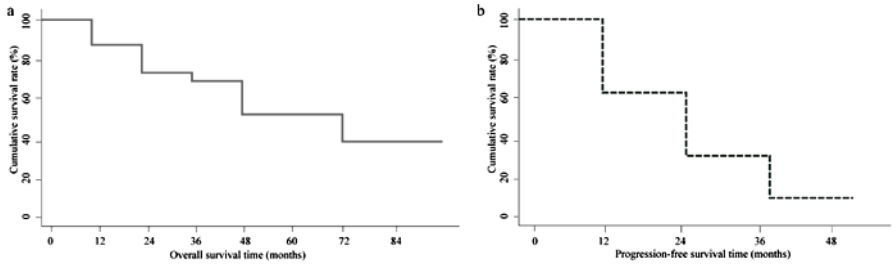

Figure 1. Survival curves of patients with brain metastasis. a, overall survival time; b, progress-free survival time.

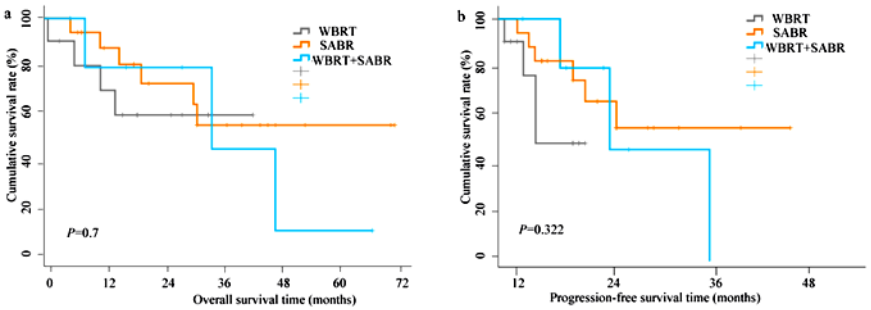

Figure 2. Survival curves of patients with brain metastasis among three radiotherapy schemes. **a,** overall survival time; **b,** progress-free survival time. WBRT, whole brain radiotherapy; SABR, stereotactic ablative radiotherapy.

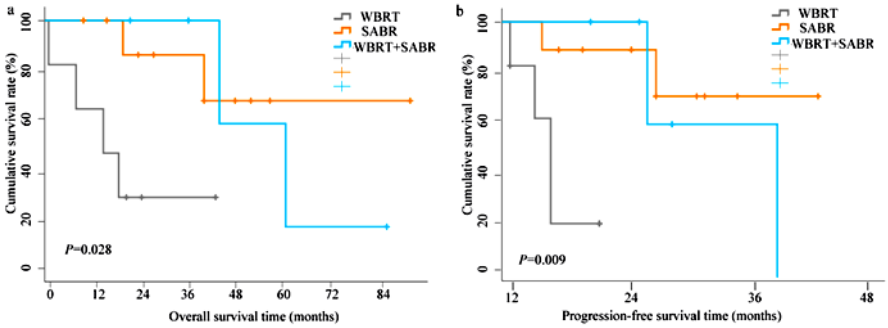

Figure 3. Survival curves of patients with brain metastasis from lung cancer among three radiotherapy schemes. **a**, overall survival time; **b**, progress-free survival time. WBRT, whole brain radiotherapy; SABR, stereotactic ablative radiotherapy.

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DISCUSSION

Malignant tumor metastasis includes oligometastasis (a single organ with five or fewer metastatic lesions or single metastasis affecting three or fewer organs) and multiple metastases (multiple metastases affecting three or more organs or a single organ with five or more metastatic lesions). In the past, patients with three or more brain metastases were often treated with WBRT and integrated boost radiotherapy. WBRT is a palliative radiotherapy that can reduce recurrence or the incidence of new metastases after treatment, but WBRT after surgery or SRS does not increase OS [18]. The NCCTGN107C/CEC.3 study showed no significant difference in OS between patients with postoperative WBRT and SRS, but the cognitive function of patients in the WBRT group was significantly decreased. For patients with brain metastases after surgery, SRS is recommended [19]. In addition, for intact metastasis, has improved the local control rate, but the quality of life of the patients in the combined treatment group significantly decreased, and their cognitive function markedly declined after SRS plus WBRT compared with SRS alone [20]. The current study findings are consistent with the above results. Patients with brain metastases from lung cancer who received SABR alone had the best prognosis, followed by patients who received WBRT+SABR, and patients who received WBRT had the worst outcomes.

Following the therapeutic landscape, the number of lesions required for oligometastasis has often been updated such that having 10 metastatic lesions is currently considered oligometastasis, and appropriate topical intervention, such as surgery or SABR, can improve the prognosis [21]. The JLGK0901 study showed no significant difference in treatment-related toxicity or side effects between patients with 2-4 brain metastases and patients with 5-10 brain metastases treated with SRS, which confirmed that patients with multiple brain metastases and good KPS scores can benefit from SRS [22]. The FIRE-SCLC Cohort Study included 710 patients with brain metastasis from small lung cancer (SCLC) and evaluated the efficacy between SRS and WBRT. The results demonstrated that the median OS and PFS were 8.5 months and 5.0 months, respectively, and the stratified assay indicated that the median OS times were 11.0 months, 8.7 months, 8 months, and 5.5 months for patients with 1 lesion, 2-4 foci, 5-10 foci, and more than 10 lesions, respectively. After propensity score matching, the median OS was 6.5 months with SRS vs 5.2 months for WBRT ($p = 0.003$), and the median PFS was 4.0 months vs 3.8 months with SRS and WBRT ($p = 0.79$) [23]. The prognosis was significantly worse in the current study; the median OS with WBRT and SRS was 25.4 months vs. 79.1 months, and the PFS was 7.1 vs. 33.4 months. All patients included in the FIRE study had small-cell lung cancer (SCLC), while most patients had non-small lung cancer (NSCLC) in the current study. In general, SCLC patients have a worse prognosis than patients with NSCLC. Moreover, patients with NSCLC have more opportunities to receive systematic therapy. In addition, the FIRE study had a longer duration (more than 10 years) than the current study, and multiple confounding factors, including technology and novel drugs, might contribute to improving the prognosis. Finally, the prognosis might be related to the irradiation dose. The guidelines prescribed for radiation doses were followed according to tumor dimension or volume: < 2 cm, 20-24 Gy/1 F; 2.1–3 cm, 18-27 Gy/1-3 F; and 3-4 cm, 15 Gy/1 F or 27-30 Gy/3 F [19, 24–28]. Alliance/CEC.3 showed that 37.5 Gy/15 F improved local control but had no OS advantage compared to 30 Gy/10 F. We noticed that the patients underwent surgical resection combined with adjuvant WBRT. Furthermore, the primary sites in the patients receiving 37.5 Gy were mainly the lung (72%) and skin (14%), whereas the patients receiving 30 Gy had lung cancer (45%), colorectal cancer (18%), and breast cancer (8%) [29]. The descriptive dose was clearly lower than that in the current study. Therefore, the optimum fraction schedule and dose require further investigation.

A comparative study of SRS and WBRT in patients with 5-15 brain metastases is still in progress [30]. The results from patients with brain metastases from lung cancer suggest that the PFS was shortened in the SRS group, but no significant difference in OS was noted between the SRS and WBRT groups [23]. The current study suggests that SABR was superior to WBRT and WBRT+SABR in terms of PFS and OS when treating patients with brain metastases from lung cancer.

The results of this study are consistent with the above studies. No significant differences in OS or PFS were identified between the WBRT, SABR, and WBRT plus SABR groups. Importantly, seriously delayed toxicity was not observed in the current study. The number of metastatic lesions was concluded to not be a key factor in defining oligometastasis, but the dose to and volume of the OARs are critical. Whether the remaining normal tissue (at least 30% of the volume) can functionally compensate for the lost volume must be considered [24].

In summary, this study showed that patients with brain metastases undergoing SABR, WBRT, and WBRT plus SABR had no significant differences in PFS or OS. SABR yielded a better prognosis than WBRT or WBRT combined with SABR for lung cancer patients with brain metastases. The sample size of this retrospective study was small, and larger, prospective studies are needed.

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***Authors' contributions*:** L.Y: conceptualization, investigation, formal analysis, visualization, and writing of the original draft; C.J: conceptualization, supervision, writing-review & editing; Z.L: data curation, investigation, analysis; H.X: conceptualization, supervision, writing-review & editing

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