ORIGINAL RESEARCH

The Impact of Hippocampal-Sparing Whole-Brain Radiotherapy on Survival and Cognitive Function in Patients with Brain Metastases

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ABSTRACT

Objective • To explore the effects on cognitive function and survival time of whole-brain intensity-modulated radiotherapy using radiotherapy equipment to protect the hippocampus.

Methods • Thirty-six patients with brain metastases treated at Qianjiang Central Hospital were enrolled in this study from January 2019 to September 2022. The patients were randomly divided into 2 groups: 15 patients received hippocampal-protection whole-brain radiotherapy, and 21 patients received conventional whole-brain radiotherapy. The Montreal Cognitive Assessment was used to evaluate the cognitive function of patients before and 24 hours, 2 months, 6 months, and 12 months after radiotherapy. Cognitive dysfunction and survival time were compared between the 2 groups.

Results • The overall mean differences in the Montreal Cognitive Assessment scores between the hippocampal-protection group and the conventional whole-brain radiotherapy group were statistically significant at 6 months (P = .006) and 12 months (P = .04) after radiotherapy. The median overall survival was 16 months (95% CI, 11.54-20.46) for the hippocampal-protection group and 14 months (95% CI, 12.9-15.21) for the conventional whole-brain radiotherapy group (P = .578). The median progression-free survival was 12 months (95% CI, 9.74-14.26) for the hippocampal-protection group and 9 months (95% CI, 6.60-11.44) for the conventional whole-brain radiotherapy group (P = .494).

Conclusion • Whole-brain radiotherapy for protecting the hippocampus can delay cognitive dysfunction in patients to some extent. (*Altern Ther Health Med.* 2024;30(1):111-115).

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INTRODUCTION

Patients with malignant tumors often develop brain metastases.[1,2] Whole-brain radiotherapy (WBRT) is an effective treatment for brain metastases,[3,4] but its adverse effects mainly lead to short-term cognitive dysfunction and memory decline. In severe cases, symptoms such as dementia may even occur.[5-7] Changes in cognitive function are thought to be caused by damage to neural stem cells in the hippocampal dentate gyrus induced by radiotherapy.[8] Hippocampal-avoidance WBRT is a method that protects the hippocampus by reducing the dose of radiation it receives while maintaining a therapeutic dose for nearby brain tissue.[9] The main techniques currently available for protecting the hippocampus during WBRT include intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), and tomotherapy (TOMO).[10] However, most radiotherapy machines are unable to perform VMAT or TOMO due to equipment limitations. Our team used IMRT technology to carry out hippocampal-avoidance WBRT and explored its impact on cognitive function, memory function, and short-term efficacy.

PATIENTS AND METHODS

Basic patient information

Thirty-six patients with solid tumors and brain metastases treated at Qianjiang Central Hospital were included in the study.

Inclusion criteria: (1) aged from 18 to 80 years, diagnosed by pathological examination and confirmed by enhanced magnetic resonance imaging of the head showing multiple intracranial metastases of malignant solid tumors (either more than 4 metastatic lesions, or less than 4 metastatic lesions but patient refusal of stereotactic radiotherapy); (2) Karnofsky Performance Scale score greater than 70 points, with an expected survival time of more than 6 months; (3) presence of neurological symptoms such as headache or dizziness; (4) no metastasis closer than 1.0 cm to the hippocampal area; (5) no contraindications for radiotherapy, and willingness to cooperate with treatment; and (6) no history of previous brain radiotherapy.

Exclusion criteria: (1) cognitive impairment due to cerebrovascular disease within 3 months; (2) diagnosis of psychiatric disorders or organic mental disorders; (3) other diseases that could affect cognitive function, such as Parkinson disease; or (4) an expected survival of less than 3 months.

The patients were randomly divided into 2 groups using a random number method: the hippocampal-protection group (treated with hippocampal-avoidance WBRT), consisting of 15 patients, and the conventional WBRT group, consisting of 21 patients. There were no statistically significant differences between the 2 groups in baseline clinical data, including sex, age, primary cancer type, Graded Prognostic Assessment score, presence or absence of brain metastatic lesions, presence or absence of extracranial metastases, number of metastatic tumors(all $P > .05$). (Table 1).

Table 1. Comparison of Baseline Clinical Characteristics

Baseline clinical characteristics	Hippocampal-protection group	Conventional whole-brain radiotherapy group	χ^2	*P* value
Sex, No.				
Male	9	13	0.0	.91
Female	6	8		
Age, No.				
≥65 years	5	6	0.1	.76
<65 years	10	15		
Primary cancer type, No.				
Lung	11	17	0.29	.59
Breast	1	4		
Ovarian	1	0		
Colon	1	0		
Esophageal	1	0		
GPA score, mean (SD)	1.825 (1.009)	1.833 (0.861)	NA	.96
Tumor metastasis to the brain, No.				
Yes	3	4	0.0	.94
No	12	17		
Other extracranial metastases, No.				
Yes	8	11	0.0	>.99
No	7	10		
Metastatic tumors, No.				
≤1 tumor	7	9	0.1	.82
>1 tumor	8	12		

Abbreviations: GPA, Graded Prognostic Assessment; NA, not applicable.

Patient interventions

All patients underwent enhanced head magnetic resonance imaging, including T1-weighted, T2-weighted, T1-weighted contrast-enhanced, and fluid-attenuated inversion recovery sequences. A radiotherapist and imaging physician jointly searched for clear metastatic tumors on the contrast-enhanced sequence cross-sections, coronal sections, and sagittal sections, recording in detail the distribution and size of metastatic tumors, maximum tumor diameter, and absence of residual tumor after treatment. The distance from each metastatic tumor to the hippocampal area was measured using the cross-sectional image closest to the hippocampus; if the hippocampus was not in the same plane, then the measurement was taken using the coronal or sagittal planes, and the distance was measured based on the center of mass of the metastatic lesion without including edematous areas.

Radiotherapy procedures

Radiotherapy positioning. Patients were laid supine on a head plate with a pillow under their head, their hands were placed at their sides, and a thermoplastic mask was used to hold their head in position. A Philips computed tomography device was used to perform the positioning scans with a layer thickness of 3 mm and a lower boundary 2 levels below the cervical vertebrae. Image data were imported into the Fonics Plan version 12.09.171117 (Chengdu Chuanda Qilin Science & Technology Co., Ltd.) treatment planning system through a regional picture archiving and communication system.

Hippocampal-protection group target area delineation. The enhanced head magnetic resonance images were imported into the picture archiving and communication system, and the positioning-enhanced CT images were retrieved in the TPS system, and the domestic Xinhua XHA600D medical linear accelerator (Shinva Medical Instrument Co., Ltd.) was used for radiotherapy. Radiotherapy target of hippocampal protection group was Sketched according to the RTOG guidelines.[11] The reference low-signal area was defined inside the medial aspect of the temporal lobe, ranging from the bottom of the crescent shape starting from the inner side of the temporal horn of the lateral ventricle upward until the low-signal area was no longer near the terminal edge of the lateral ventricle; the hippocampus dose-limiting region was defined as the area 3 mm outside the hippocampus border, while brain metastases were contoured and defined as the gross tumor volume, which was expanded 3 mm to form the planning gross tumor volume. The entire brain excluding the hippocampus dose-limiting region was designated the clinical target volume, which was expanded 3 mm to form the planning target volume; the bilateral crystalline lenses, eyeballs, and optic nerves were also delineated. The target volumes were confirmed by a senior radiotherapist and physicist.

Hippocampal-protection group plan design and evaluation. Planning design was performed on the treatment planning system using 6 MV x-rays for a 9-field design with coplanar field angles of 200°, 240°, 280°, 320°, 0°, 40°, 80°, 120°, and 160°. The whole-brain prescription dose was 3 Gy/fraction, delivered 10 times. The plan was approved when more than 95% of the planning target volume received at least 95% of the prescribed dose.

The homogeneity index (HI) was calculated as HI = D2%/D98%. The organs-at-risk limits were as follows: crystalline lens, less than 5 Gy; mean eyeball dose, less than 35 Gy; and optic nerve dose, less than 54 Gy.

Conventional WBRT group method. Conventional WBRT was administered using 2-field, 3-dimensional conformal radiotherapy with the clinical target volume planned as the entire brain plus an additional expansion of 3 mm to create the planning target volume using the same dose as for the hippocampal-protection group. The target volumes of the WBRT group were confirmed by a senior radiotherapist and physicist.

Evaluation criteria for patient response and survival

The patients had a comprehensive re-examination every 3 months after treatment completion, including cranial examination by enhanced head magnetic resonance imaging, and were evaluated using the RECIST (Response Evaluation Criteria in Solid Tumours) version 1.1 criteria[12]: complete response, no evidence of the target lesions; partial response, a decrease in the sum of the diameters of all target lesions by at least 30% relative to baseline; progression disease : The sum of all target lesion diameters increased by at least 20% or new lesions appear compared to the target lesion diameter and minimum value.; and stable disease, a change in the sum of the baseline lesion diameters that does not meet the threshold for partial response or progressive disease.

Cognitive function assessment

The Montreal Cognitive Assessment (MoCA) was used to test patients' short-term memory and cognitive function within 24 hours before WBRT and within 24 hours and at 2 months, 6 months, and 12 months after WBRT.

Statistical analysis

SPSS version 19.0 software was used for data processing and analysis. The log-rank test was used to evaluate survival curves, and the χ^2 test was used to evaluate the intergroup efficacy. Quantitative data are expressed as mean (SD). $P < .05$ indicated a statistically significant difference between groups.

RESULTS

Comparison of MoCA scores before and after radiotherapy

There were no significant differences in MoCA scores between the hippocampal-protection group and the conventional WBRT group before radiotherapy, and 24 hours and 2 months after radiotherapy ($P > .05$). Within each group, pairwise comparisons showed a slow decline in MoCA scores after radiotherapy with respect to before radiotherapy; the differences were statistically significant at 6 months and 12 months after radiotherapy ($P < .05$) (Table 2).

Survival assessment

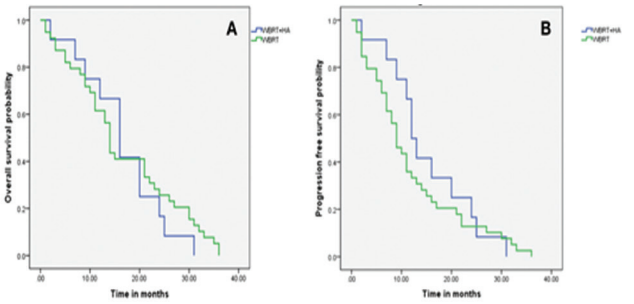
The 36 patients were comprehensively reviewed every 3 months after radiotherapy for 12 months. The median overall survival was 16 months (95% CI, 11.54-20.46) for the hippocampal-protection group and 14 months (95% CI, 12.9-15.21) for the conventional WBRT group. The median progression-free survival was 12 months (95% CI, 9.74-14.26) for the hippocampal-protection group and 9 months (95% CI, 6.60-11.44) for the conventional WBRT group. There were no statistically significant differences in PFS (P = .494) and OS (P = .578) between the two groups (Figure 1).

Table 2. Comparison of Montreal Cognitive Assessment Scores Before and After Radiotherapy

Time from radiotherapy	Montreal Cognitive Assessment scores ,mean (SD)		*P* value
	Hippocampal-protection group, (n = 15)	Conventional whole-brain radiotherapy group, (n = 21)	
≤24 hours before	28.80 (1.01)	28.00 (1.70)	.16
≤24 hours after	28.60 (1.30)	28.05 (1.77)	.38
2 months after	23.73 (2.09)[a]	24.19 (1.86)[a]	.42
6 months after	26.60 (1.92)[a]	24.48 (2.36)[b]	.006
12 months after	26.40 (2.44)[a]	24.95 (1.94)[b]	.04

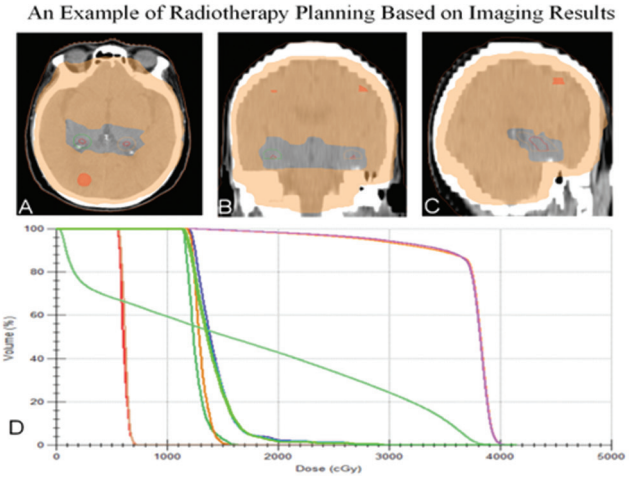
[a]Montreal Cognitive Assessment scores at different time points after radiotherapy in the same group vs preradiotherapy scores.
[b]Preradiotherapy Montreal Cognitive Assessment scores vs postradiotherapy scores at the same time point.

Figure 1. A. Overall Survival, B. Progression-Free Survival Curves



Abbreviations: WBRT-HA, hippocampal avoidance whole-brain radiotherapy; WBRT, whole-brain radiotherapy.

Figure 2. A-C, Radiotherapy plan of a 65-year-old woman with non-small cell lung cancer with five brain metastases, the orange area represents the area covered by 90% of the dose,the pink area respresents gross tumor volume,the red area reapresents hippocampal. A: CT cross-sectional bitmap; B: CT coronal bitmap; C: CT sagittal bitmap. D, Cumulative dose-volume histogram.



DISCUSSION

Advances in modern medical technology have helped increase the survival time of patients with malignant tumors, but this comes with an increased probability of brain metastasis. WBRT is effective at treating solid tumor brain metastases. However, with the development of stereotactic radiosurgery, stereotactic radiotherapy, and various new antitumor drugs, the relevance of WBRT for the treatment of brain metastases has been challenged.[13] Research by Tsao et al[14] showed that stereotactic radiosurgery is better for local control in patients with up to 3 brain metastases and has fewer side effects. Hughes reported stereotactic radiosurgery is not inferior to WBRT in terms of efficacy in patients with up to 15 brain metastases and can thus replace WBRT.[15] However, stereotactic radiosurgery cannot reduce intracranial pressure quickly nor prevent the occurrence of new intracranial metastases; because of the high irradiation dose involved, there is a higher probability of radiation-induced brain necrosis from stereotactic radiosurgery while also requiring expensive equipment and advanced technical knowledge.[16]

The hippocampus is located on the ventral medial side of the temporal lobe and is mainly responsible for learning and memory functions. This part of the brain is very sensitive to radiation exposure, and the degree of cognitive dysfunction correlates positively with the irradiation dose.[17,18] Limiting the hippocampal dose during WBRT can effectively control intracranial lesions while preventing or reducing cognitive impairment and delaying recurrence, thereby improving patient quality of life.

Currently available techniques for preserving the hippocampus during WBRT include IMRT, VMAT, and TOMO. Gondi et al[19] showed that both IMRT and TOMO can achieve hippocampal protection during WBRT, but IMRT is worse than TOMO in terms of in terms of the conformity index. Two studies by Marsh et al[20,21] found that the use of IMRT or TOMO for hippocampal protection during WBRT for gliomas can reduce the dose to normal brain tissue while preserving tumor target area doses; they also found that IMRT has an advantage over TOMO in reducing the radiation dose to affected brain lesions. Li et al[22] showed that inverse single-arc VMAT technology has advantages over IMRT in terms of target uniformity, number of device hops, and treatment time, but its use is limited by the patient's economic situation and organ-at-risk factors.

We used IMRT to treat patients with solid tumors who had more than 4 intracranial metastases or those who refused stereotactic radiosurgery and had no metastatic tumors within 1 cm beyond the hippocampus. Our use of hippocampal-avoidance WBRT (Figure 2) resulted in a significantly lower maximum dose to the hippocampal region in patients receiving hippocampal protection than in those without such protection. Thus, hippocampal-avoidance WBRT demonstrated an advantage over the IMRT plan that lacked hippocampal dose limitation.

The cognitive function of patients in the hippocampal-protection group and the conventional WBRT group demonstrated a sustained, slow decline after radiotherapy. The degree of decline in cognitive function was more moderate in patients in the hippocampal-protection group than in the conventional WBRT group, and there was a statistically significant difference between the 2 groups at 6 months and 12 months after the completion of radiotherapy.

Oehlke et al[23] found that the median progression-free survival for patients who underwent hippocampal-avoidance WBRT was 40 weeks, and the median overall survival reached 71.5 weeks; they showed that using radiotherapy equipment for protecting the hippocampus during WBRT resulted in a median overall survival of 16 months and a median progression-free survival of 12 months. In our study, no decrease was observed in the local control rate among patients who underwent hippocampal-protective WBRT compared with those who received conventional treatment; moreover, there were no statistically significant differences in PFS and OS between the two groups (Figure 1). This also confirms that hippocampus-protected whole-brain modulated arc therapy does not increase the risk of intracranial lesion progression.

In conclusion, the use of WBRT with hippocampal protection can delay cognitive dysfunction in patients to a certain extent. However, clinical data are limited, and further clinical trials are needed to verify our results.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

XL and CL led the conception and design of this study. YL, JD, BY, ZY and YW were responsible for the data collection and analysis. YL and JD were in charge of interpreting the data and drafting the manuscript. XL and CL made critical revisions for important intellectual content. The final version was read and approved by all the authors.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of The Affiliated Qianjiang Hospital of Chongqing University (Chongqing, China). Signed informed consents were obtained from the patients and/or their guardians.

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