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Hyperbaric oxygen therapy enhances restoration of physical functional in patients with recurrent glioma: A case report

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Abstract. Patients with recurrent glioblastoma often opt for hypofractionated stereotactic radiosurgery, which can cause various adverse reactions. The pharmacological interventions used to manage these adverse reactions are usually unsatisfactory. The present study reports the case of a patient with recurrent glioblastoma who underwent hyperbaric oxygen therapy followed by immediate hypofractionated stereotactic radiosurgery. Grip strength, isokinetic muscle testing and gait analysis were evaluated during the treatment period, spanning an interval of 7 days in March 2023. Assessments before and after treatment revealed improvements in all three parameters compared with pre-treatment levels. In summary, combining hyperbaric oxygen therapy with hypofractionated stereotactic radiosurgery may enhance muscle strength in patients with recurrent glioblastoma. This treatment approach can lead to significant improvements in gait parameters, promoting better motor coordination. Furthermore, the combined therapy could offer a promising alternative for managing muscle weakness and mobility issues after glioblastoma recurrence.

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Abbreviations: CTV, clinical target volume; FiO_2, fraction of inspired oxygen; GTV, gross tumor volume; MRI, magnetic resonance imaging; OS, overall survival; PTV, planning target volume

Key words: gait, grip strength, hyperbaric oxygen therapy, hypofractionated stereotactic radiosurgery, isokinetic muscle strength, recurrent glioma

Introduction

High-grade gliomas, representing >50% of all gliomas (1), predominantly affect middle-aged adults (2). Despite treatment, 90% of patients experience local recurrence (3), leading to a poor prognosis in patients with high-grade glioma upon recurrence (4). Those undergoing secondary surgery and chemotherapy have a median overall survival (OS) time of 6-10 months (5). The therapeutic efficacy of programmed cell death protein 1 inhibitors alone or in combination with bevacizumab in recurrent glioblastoma has proven to be unsatisfactory (6). Moreover, conventional radiotherapy has demonstrated limited effectiveness for recurrent glioblastoma, with a median OS time of 7.0 months and a median progression-free survival (PFS) time of 2.8 months (7). However, hypofractionated stereotactic radiosurgery has shown promise in improving both local PFS (LPFS) and OS times in patients with recurrent glioma, with reported median LPFS and OS times of 8.1 and 11.4 months, respectively (8). A retrospective study indicated that patients who opted for hypofractionated stereotactic radiosurgery achieved a median OS time of 17.6 months (9).

While radiation therapy can control tumor growth, it may lead to adverse effects, such as fatigue, increased intracranial pressure and delayed reactions (10). This increases the burden on caregivers, who face limited effective strategies to manage patient reactions beyond advising rest. Treatment usually involves administering drugs such as dexamethasone, mannitol and bevacizumab to lower intracranial pressure and alleviate radiation side effects. However, these interventions do not improve clinical symptoms such as muscle weakness and gait coordination (11,12). Evidence indicates that hyperbaric oxygen therapy may mitigate radiation-induced brain injury in cases of brain metastases (13). A preliminary study suggested that post-hyperbaric oxygen therapy combined with radiotherapy could offer some therapeutic effects for recurrent glioblastoma (14). Nevertheless, there is a lack of research on the potential of hyperbaric oxygen therapy combined with radiotherapy to improve clinical symptoms in patients with recurrent glioblastoma. The present case aims to highlight new therapeutic approaches for such patients and help provide better treatment modalities for them in the future.

Case report

Patient treatment process. In this case study, the recurrence of a high-grade glioma in a 37-year-old male patient was managed. The patient initially presented with dizziness in December 2020, and magnetic resonance imaging (MRI) at Huai'an First People's Hospital (Huai'an, China) revealed a possible glioma in the right temporal lobe. In February 2021, a right thalamic tumor resection was performed at Huashan Hospital (Shanghai, China), revealing a diffuse high-grade glioma in the right thalamus and hippocampus, with H3K27M mutation (as detected by genetic testing). According to the World Health Organization grading system (15), the tumor was classified as at least grade III. After surgery, the patient experienced mild left-sided hemiparesis. In March 2021, the patient underwent postoperative adjuvant radiotherapy at a dose of 60 Gy in 30 sessions, along with oral chemotherapy using 140 mg/day of temozolomide, over a total treatment period of 42 days. A follow-up MRI scan in November 2022 showed recurrence in the right frontal lobe. Subsequently, the patient received an intravenous infusion of 400 mg bevacizumab within 1 day in December 2022, January 2023 and February 2023, respectively. For 7 days in March 2023, the patient underwent hypofractionated stereotactic radiosurgery (CyberKnife®) for the recurrent lesion in the right frontal lobe, with a dose of 25 Gy delivered in 5 fractions. Hyperbaric oxygen therapy was administered before each radiotherapy session. The treatment concluded after the fifth radiotherapy session. Fig. 1 shows the radiotherapy target area, with the treatment site.

Physical function assessment. Grip strength and motor function were assessed during hospitalization. The grip strength assessment involved the use of an electronic dynamometer. The participant stood upright with feet naturally separated and arms hanging freely. The participant gripped the dynamometer with one hand as forcefully as possible, squeezing it three times for a minimum of 5 sec each time. The displayed values were recorded to determine the average grip strength.

Motor function evaluations included isokinetic strength testing and gait assessment. Isokinetic strength testing involved using a Biodex Multi-Joint Isokinetic Dynamometer system (Biodex Medical Systems) to measure concentric muscle strength in the lower limbs at the knee joint. Before the test, the torque produced by the limb weight was neutralized, and the participant underwent three practice trials to get acquainted with the movements. The range of motion spanned from 90˚ of knee flexion to full extension, with an angular velocity of 60˚/sec. The participant executed 10 maximal concentric extensions and flexions, with a 180-sec rest period between different velocity test sets.

Gait assessment utilized a three-dimensional gait analysis system to measure spatiotemporal parameters precisely. Key variables included step frequency (steps/min), step length (meters), stride length (meters) and walking speed (m/sec).

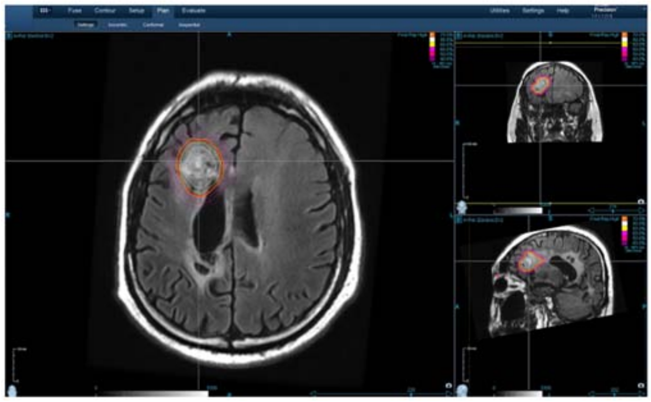

Figure 1. Target image for patients with recurrent gliomas undergoing hypofractionated stereotactic radiosurgery (CyberKnife®).

Gait analysis, grip strength and isokinetic testing offer a comprehensive and accurate evaluation of changes in muscle function and motor ability in patients with recurrent glioblastoma before and after treatment, providing multidimensional data that are valuable for research.

Hypofractionated stereotactic radiosurgery. Hypofractionated stereotactic radiosurgery was performed using a Radiosurgery System (Accuray, Inc.). The patient was immobilized with a custom thermoplastic mask and underwent computed tomography scanning with a slice thickness of 1.25 mm, as well as MRI examination with a slice thickness of 2 mm, encompassing T1-weighted contrast-enhanced and T2 fluid attenuated inversion recovery images. The planning system fused these images to delineate the tumor contours, involving radiation oncologists, neurosurgeons and medical physicists in the tumor delineation, planning and dose selection processes.

The gross tumor volume (GTV) was defined as the tumor on T1-weighted sequences, where the clinical target volume (CTV) was equivalent to the GTV. The planning target volume (PTV) was a uniform 2-mm expansion of the CTV. Inverse planning using Multiplan software (version 4.6; Accuray, Inc.) determined the prescription dose for the PTV based on the target volume, location, prior irradiated volume, total dose and treatment intervals.

Hyperbaric oxygen therapy. Hyperbaric oxygen therapy was administered in a hyperbaric chamber. The procedure involved pressurization for 17 min at 0-2 ATA, followed by a 20-min compression period with a fraction of inspired oxygen (FiO_2) >90% and a 5-min rest. After three cycles of oxygen inhalation, a 23-min decompression phase with FiO_2 >90% was performed. The total duration of treatment was 115 min.

Assessment results. Assessments were conducted both before the first hyperbaric oxygen therapy session and after the completion of the radiotherapy cycle.

Grip strength assessment. This study assessed grip strength in both hands before and after treatment. Grip strength was measured three times for each hand, and average values were calculated. Before the treatment, the left hand had grip strengths of 20.9, 18.8 and 15.2 kg, with a mean of 18.3 kg. The right hand had grip strengths of 28.4, 30.6 and 26.2 kg,

Table I. Isokinetic muscle strength testing for patients before the start and after the completion of the treatment cycle.

	Extension				Flexion			
	Pre-treatment		Post-treatment		Pre-treatment		Post-treatment	
Parameter	Right	Left	Right	Left	Right	Left	Right	Left
Peak torque, N·m	103.5	100.1	118.7	92.4	54.1	33.1	63.6	65.1
Time to peak torque, msec	670	550	620	630	550	960	690	1,770
Angle for peak torque, ˚	77	73	78	73	55	69	58	64
Total work, joules	724.7	427.7	899.6	548.4	438.6	86.4	538.5	367.1
Mean power, watts	36.7	31.7	47.5	36.3	18.4	5.8	26.1	19.3
Work fatigue, %	-47.4	54.3	-1.7	-48.7	-65.5	-2.5	22.1	22.0
Acceleration time, msec	90	60	70	100	80	390	120	1,310
Deceleration time, msec	840	310	820	190	890	390	630	260

with a mean of 28.4 kg. After treatment, the left hand showed improvement with grip strengths of 22, 21.7 and 21.1, with a mean of 21.6 kg. The right hand also showed improvement with grip strengths of 33.8, 33.2 and 30.4 kg, with a mean of 32.5 kg. This indicates a marked improvement in grip strength after treatment completion.

Isokinetic muscle testing. Following treatment, isokinetic strength testing showed a decrease in the peak torque of the left knee extensors from 100.1 to 92.4 N·m, while an increase was observed in the peak torque of the left knee flexors, and both right knee flexors and extensors. Additionally, both the total work and average power of knee joint movement increased. The acceleration time for knee extension in the right lower limb decreased from 90 to 70 msec, while the acceleration times for knee flexion in the left lower limb and knee extension in the right lower limb increased. Furthermore, the deceleration time for knee extension on both sides decreased (Table I).

Gait assessment. Post-treatment gait analysis revealed that the patient had a higher pre-treatment step frequency (117 steps/min). Compared with the reference value, the left lower limb exhibited a shorter step size of 47 cm, while the right lower limb had a step size of 62 cm. After treatment, both step sizes normalized. There was also a minor decline in the double support phase, decreasing from 6.95 and 9.77% to 5.59 and 8.9%, respectively (Table II). This suggests that the gait of the patient improved and became more symmetrical after treatment. The overall gait patterns of the patient also showed a decrease in variability. These results indicate marked progress in gait and motor control, demonstrating the effectiveness of the treatment in improving gait patterns.

Discussion

Hyperbaric oxygen therapy is commonly used to treat hypoxic conditions, such as carbon monoxide poisoning, decompression sickness, cerebral embolism and gas gangrene (16). Emerging evidence suggests its potential as an anticancer therapy, particularly in targeting hypoxic tumor microenvironments, which are significantly associated with heightened cancer invasiveness (17,18). In cancer treatment, the low oxygen levels in tumor cells contribute to the ineffectiveness of radiotherapy and chemotherapy (19). Glioblastoma tissue, characterized by impaired microcirculation and anaerobic metabolism, exemplifies a tumor that may benefit from hyperbaric oxygen therapy via oxygen-induced cell apoptosis (20-22). High-grade glioma cells exhibit anaerobic metabolism (23), with lower oxygen consumption compared with normal brain cells (24). In biological tissues, the effect of radiation is greatly affected by the presence or absence of molecular oxygen (25). Preliminary studies indicated a rapid decrease in oxygen tension in normal brain tissue following hyperbaric oxygen therapy, while oxygen tension dropped more slowly in high-grade glioma cells. This finding supports initiating radiotherapy promptly after hyperbaric oxygen therapy. Post-hyperbaric oxygen therapy radiotherapy avoids radiation-induced damage to normal cells and increases the radiosensitivity of high-grade glioma cells (26,27).

Notably, researchers have proposed the 'hyperoxia-hypoxia paradox', which posits that cellular metabolic changes typically triggered by hypoxia can also be induced by intermittent hyperoxic conditions. This concept may explain the neuroprotective effect and neurorecovery effects observed in certain studies (28,29). Particularly, hyperbaric oxygen therapy has been shown to stimulate neural stem cell proliferation and enhance myoblast growth, promoting muscle regeneration (30-32). Furthermore, intermittent hyperbaric exposure during exercise training has been reported to improve endurance performance by promoting oxidative and glycolytic capacity, as well as upregulating proteins involved in mitochondrial biosynthesis within striated muscles (33).

Hyperbaric oxygen therapy elevates blood oxygen levels, potentially aiding in the healing of ligament and muscle injuries caused by oxygen depletion during exercise (34), and alleviating muscle fatigue induced by plantar flexion movements (35). Research indicates that hyperbaric oxygen therapy relieves muscle soreness caused by eccentric contraction of the quadriceps femoris muscle and injury induced by eccentric contraction of the fibularis longus muscle (36). However, it does not have a recovery effect on muscle soreness caused by eccentric contractions of the elbow flexors and knee flexors (37-39). Currently, there is limited research on the use of hyperbaric

Table II. Gait assessments for patients before the start and after the completion of the treatment cycle.

	Measured value		
Parameter	Pre-treatment	Post-treatment	Reference value[a]
Step frequent, steps/min	117.00	103.30	97.07-112.30
Gait period, sec	2.05	2.32	0.98-1.22
Stride, cm	109	109	102-138
Step speed, m/sec	0.53	0.47	
Step deviation, cm	15	7	
Double support phase, %			
1st phase	6.95	5.59	6.14-16.28
2nd phase	9.77	8.90	6.14-16.28
Step size, cm			51-69
Left	47	51	
Right	62	58	
Max. hip flexion, ˚			
Left	35.33	35.54	
Right	53.36	46.00	
Max. hip extension, ˚			
Left	15.04	12.19	
Right	29.91	23.97	
Max. knee flexion, ˚			
Left	66.54	70.33	
Right	76.46	70.61	
Max. knee extension, ˚			
Left	1.88	3.54	
Right	25.88	20.14	
Max. ankle dorsiflexion, ˚			
Left	23.07	23.40	
Right	19.82	16.65	
Max. ankle plantar flexion, ˚			
Left	17.59	15.92	
Right	21.35	19.79	
Support phase, %			54.11-67.00
Left	57.68	56.65	
Right	59.43	58.50	
Swing phase, %			33.94-45.00
Left	42.32	43.35	
Right	40.57	51.50	

[a]Certain indicators have different reference values depending on the patient's height and weight, and these are therefore not specifically stated. Moreover, these indicators only need to be compared before and after to evaluate the treatment effect, so there is no reference value for these indicators. Max, maximum.

oxygen therapy to alleviate muscle fatigue, indicating the need for further investigations to establish its efficacy in this regard.

Multiple studies have indicated that combining hyperbaric oxygen therapy with radiotherapy can extend the survival time and improve the prognosis in patients with glioblastoma (40-42). Importantly, this combination does not increase adverse effects in patients (43), instead, hyperbaric oxygen therapy reduces intracranial pressure, alleviates headache symptoms (44), and improves cognitive function and focal neurological deficits in patients undergoing radiotherapy (13,45,46). Additionally, it enhances the long-term quality of life in patients with late-stage severe radiation toxicity by improving physical function, daily activities and overall subjective health status (47). Although retrospective studies indicate an adverse event rate of 0.68% for hyperbaric oxygen therapy, with barotrauma and confinement anxiety being the most frequently reported, these events are generally mild (48).

The present case report provides evidence that the immediate application of hypofractionated stereotactic radiosurgery following hyperbaric oxygen therapy improves muscle strength and motor coordination in patients with recurrent glioblastoma. While these findings offer valuable insights into the clinical treatment of affected individuals, the single-case nature of this study and the absence of a control group limits the generalizability of the results. Further investigations with larger sample sizes are warranted to validate the findings. Additional cases are currently being collected for ongoing research.

The patient had no adverse reactions during and after the treatment, and is quite satisfied with the effect of the hyperbaric oxygen therapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TTC, XW and YLZ were responsible for conceptualization. TTC, TJ, YG and WZ contributed to designing the study and collecting clinical information. TTC, TJ and YG wrote and revised the manuscript. WZ, XW and YLZ reviewed and edited the manuscript. XW and YLZ confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Huashan Hospital (approval no. KY2019-525). The patient was informed about the treatment modality and provided written informed consent.

Patient consent for publication

Informed consent was obtained from the patient for the publication of this case report, including the publication of all images, clinical data and other data included in the manuscript.

Competing interests

The authors declare that they have no competing interests.

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