

# Hyperbaric oxygen therapy as an adjunct treatment for glioma and brain metastasis: a literature review

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## Abstract

The incidence and mortality rates of malignant tumors are increasing annually, with gliomas and brain metastases linked to a poor prognosis. Hyperbaric oxygen therapy is a promising treatment modality for both gliomas and brain metastases. It can alleviate tumor hypoxia and enhance radiosensitivity. When combined with other treatments for gliomas, this therapy has the potential to enhance survival rates. This review addresses the progress in research on the use of hyperbaric oxygen therapy combined with radiotherapy. For brain metastases, the combination of hyperbaric oxygen therapy and stereotactic radiosurgery is both feasible and advantageous. This combination not only offers protection against radiation-induced brain injury but also supports the recovery of neurological and motor functions. The incidence of adverse reactions to hyperbaric oxygen therapy is relatively low, and it is safe and manageable. Future efforts should be made to investigate the mechanisms by which hyperbaric oxygen therapy combined with radiotherapy treats gliomas and brain metastases, optimize protection of the combined treatment against brain injury, minimizing adverse reactions, conducting multidisciplinary research and clinical trials, and training healthcare providers to facilitate broader clinical application.

**Key Words:** brain injury; brain metastases; cerebral protection; gliomas; hyperbaric oxygen therapy; motor functions; radiation necrosis; radiotherapy

## Introduction

Currently, the incidence and mortality rates of malignant tumors are increasing.<sup>1</sup> Tumors of the central nervous system constitute 1.4% of all malignant neoplasms.<sup>2</sup> Gliomas account for 60% of all primary brain tumors. Among gliomas, approximately 80% are high-grade gliomas of advanced nature, and 20% are low-grade gliomas.<sup>3</sup> High-grade glioblastomas present a rather dismal prognosis. The median survival time following surgery in combination with radiotherapy and chemotherapy is limited, and the local recurrence rate is remarkably high.<sup>4,5</sup> Following radiotherapy, there is a high likelihood of developing brain injury and necrosis.<sup>6</sup> As reported, twenty percent of cancer patients will experience brain metastases. The majority of brain metastases are derived from lung cancer, breast cancer, colorectal cancer, melanoma, and renal cell carcinoma.<sup>7</sup> Brain metastases portend a dismal prognosis, with a limited survival span. They give rise to symptoms of elevated intracranial pressure, thereby detrimentally impacting the quality of life of patients.<sup>8</sup> Owing to the presence of the blood–brain barrier, the efficacy of conventional chemotherapy is suboptimal.<sup>9,10</sup> Although targeted medications exhibit favorable effects in controlling intracranial metastatic tumors, they can be utilized only when the driver gene is positive.<sup>11</sup> When patients present with brain metastases, radiotherapy is typically used. It can mitigate symptoms and restrain progression; however, it cannot increase the overall survival time of patients.<sup>12</sup>

Hyperbaric oxygen therapy (HBOT) is defined as a medical treatment modality wherein the patient is entirely placed within a pressure chamber and inhales 100% oxygen at an absolute pressure exceeding 1 atmosphere (ATA; 1 ATA = 101.325 kPa).<sup>13</sup> In normal situations, oxygen in the blood is predominantly transported in combination with hemoglobin. However, under hyperbaric oxygen conditions, a significant quantity of oxygen exists in the plasma in

a physically dissolved form, which can promptly improve the state of tissue oxygen deficiency.<sup>14,15</sup> Hyperbaric oxygen is typically used to treat hypoxic disorders, such as carbon monoxide poisoning, decompression sickness, cerebral embolism, and gas gangrene.<sup>16</sup> Hyperbaric oxygen may induce contraction of cerebral blood vessels and reduce cerebral blood flow, thereby mitigating cerebral edema and decreasing intracranial pressure.<sup>17,18</sup>

In the treatment of tumors, hyperbaric oxygen can mitigate adverse reactions following radiotherapy for head and neck neoplasms.<sup>19</sup> It can also manage radiation-induced injury to the rectal mucosa in patients with rectal carcinoma and cervical carcinoma.<sup>20</sup> Hyperbaric oxygen has an inhibitory effect on breast cancer and can reduce tumor growth. However, cervical and bladder cancers appear to be unresponsive to this treatment modality.<sup>21</sup> In glioblastomas, hyperbaric oxygen in conjunction with radiotherapy and chemotherapy can increase survival duration and mitigate radiation-induced cerebral injury and necrosis.<sup>22,23</sup> In cases of brain metastases, HBOT can augment therapeutic efficacy.<sup>24</sup> Currently, preferable outcomes have been reported in the study of hyperbaric oxygen in combination with radiotherapy and chemotherapy in glioblastomas,<sup>25-27</sup> yet it is still sparingly utilized in clinical therapeutics. Research on hyperbaric oxygen in brain metastases is rather limited, and we need to delve deeper into this treatment approach. This narrative review aims to provide an overview of the research advancements in the use of hyperbaric oxygen combined with radiotherapy for treating glioblastomas and brain metastases.

## Search Strategy

In September 2024, the author retrieved relevant literature by electronically searching the PubMed database. The search strategy and selection criteria utilized the following keywords: hyperbaric

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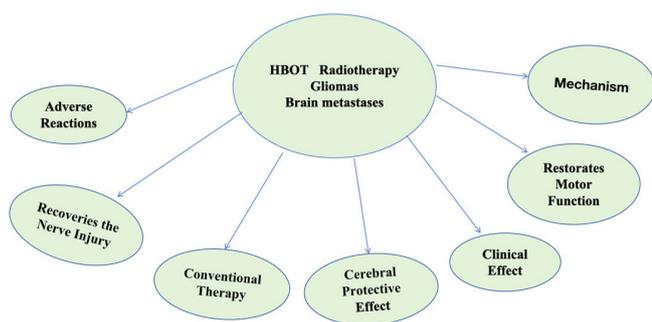
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oxygen therapy, gliomas, brain metastases, radiotherapy, radiation-induced brain injury, radiation-induced brain necrosis, neurological and motor function impairment, adverse reactions to hyperbaric oxygen and neuroprotection. Various combinations of these search terms were employed to conduct a comprehensive literature review. We examined the relevance of the titles and abstracts to our target content. If they were deemed relevant, the entire paper was consulted to ensure that there were appropriate descriptions of hyperbaric oxygen-related events. The inclusion criteria included original studies, case reports, systematic reviews, and meta-analyses published in English. Abstracts standing alone, articles with duplicated data, and those lacking original data were excluded. Publications that failed to meet specific research criteria or lacked clear research methods were also excluded. Most of the selected literature (accounting for 90% of all references) was published between 2000 and 2024. The articles considered in this review are summarized in **Figure 1**.



**Figure 1 | Classification of contents after screening relevant articles in this review.**

This review explores the multifaceted effects of hyperbaric oxygen therapy (HBOT) in the context of radiotherapy for gliomas and brain metastases, specifically, its clinical efficacy, mechanism of action, adverse reactions, impact on nerve injury and role in motor function recovery.

### Conventional Therapy for Glioblastomas and Brain Metastases

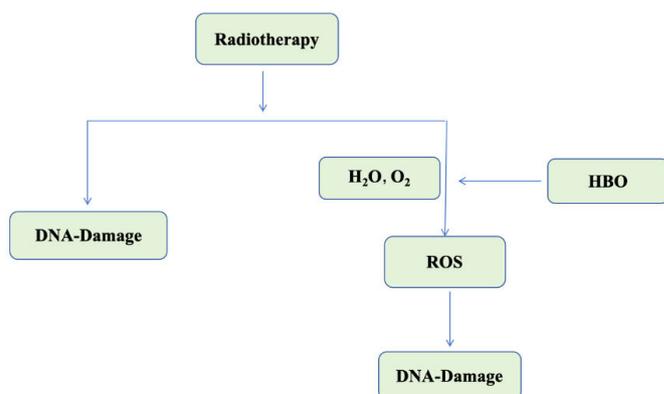
Glioblastomas are solid neoplasms; in terms of structure, the blood vessels are typically dilated, featuring tortuous courses and uneven distribution, leading to a scarcity of blood vessels in certain regions within the tumor and a notable increase in interstitial fluid pressure, aggravating hypoxia and acidosis within the tumor.<sup>28</sup> Hypoxia activates the hypoxia-inducible factor pathway accountable for regulating crucial cell cycle genes,<sup>29</sup> additionally induces the formation of new vasculature,<sup>30,31</sup> and augments the metastatic potential of tumor cells, whereby the tumor cells display enhanced aggression.<sup>32</sup> The oxygen partial pressure in normal tissues ranges from 24 to 66 mmHg, while in solid tumors, it ranges from 2.5 to 30 mmHg.<sup>33</sup> Compared with normal brain cells, high-grade glioma cells exhibit anaerobic metabolism and a lower oxygen consumption rate.<sup>34,35</sup> The hypoxic microenvironment is capable of coordinating the proliferation and treatment resistance of glioblastoma stem cells not only because the nutritional constraints imposed by hypoxia initiate adaptive mechanisms within glioblastoma stem cells, leading them to transition toward aerobic glycolysis,<sup>36</sup> but also because it induces them to enter a quiescent state, which further gives rise to resistance to chemotherapy and radiotherapy.<sup>37,38</sup> Under hypoxic circumstances, quiescent glioblastoma stem cells may also transform toward more mesenchymal-like traits, leading to increased migration and invasion.<sup>39,40</sup>

Despite the presence of the blood–brain barrier and the blood–cerebrospinal fluid barrier in the brain, malignant neoplasms still breach the blood–brain barrier via diverse means.<sup>40,41</sup> Once the blood–brain barrier is penetrated, tumor cells disseminate via multiple routes, migrating along the exterior of the leptomeninges and parenchymal blood vessels, traversing between the surfaces that demarcate brain regions, and within the cerebrospinal fluid.<sup>42</sup> The H2O30-BrM3 lung-derived brain metastasis model in rats indicates that hypoxia exists in the microenvironment of brain metastases and results in hypoxia-related metabolic/oxidative alterations.<sup>43</sup> Hypoxia gives rise to the resistance of brain tumors to radiotherapy, thus hindering the attainment of an optimal therapeutic outcome.<sup>44</sup>

The principal mechanism of radiotherapy lies in inducing DNA damage either by directly depositing ionizing energy into DNA or through the generation of free radicals.<sup>45</sup> However, the majority of DNA damage is caused by the production of free radicals. Under irradiation, water molecules undergo radiation-induced decomposition to form unstable hydrogen and hydroxyl radicals. The hydrogen radical reacts with molecular oxygen to generate unstable perhydroxyl radicals and hydrogen peroxide, namely, reactive oxygen species. This results in severe damage to DNA strands and ultimately leads to cell death.<sup>46,47</sup>

### Methods and Effects of Hyperbaric Oxygen Therapy for Glioma and Brain Metastases

The standard regimen for HBOT prescribes that patients inhale pure oxygen (approximately 100%) within a hyperbaric chamber at an absolute pressure between 1.5 and 2.5 ATA. In this context, the absolute pressure is defined as the total atmospheric pressure and the gauge pressure inside the hyperbaric chamber.<sup>48</sup> Hyperbaric oxygen positively influences the oxygenation of brain tissues. In both normal brain tissues and glioblastoma tissues, the oxygen level can increase by 100–115% following exposure to hyperbaric oxygen, ameliorating the hypoxic conditions within tumor tissues and increasing sensitivity to radiotherapy.<sup>49,50</sup> The mechanisms by which hyperbaric oxygen increases sensitivity to radiotherapy are shown in **Figure 2**. Following HBOT, the oxygen tension in normal brain tissues decreases rapidly. In contrast, the oxygen tension in high-grade gliomas decreases at a slower pace. HBOT increases the partial pressure of the oxygen level in the tissue immediately adjacent to the tumor and within the tumor itself.



**Figure 2 | Biological mechanisms of hyperbaric oxygen in increasing radiotherapy sensitivity.**

The direct effect of radiotherapy is to damage the DNA of tumors, whereas its indirect effect is to damage the DNA of tumors by generating ROS. Hyperbaric oxygen can promote the formation of ROS and enhance the ability of radiotherapy to damage the DNA of tumor cells. HBO: Hyperbaric oxygen; ROS: reactive oxygen species.

Additionally, within 15 minutes after decompression, the partial pressure of oxygen in these two areas remains at or above 30 mmHg.<sup>51</sup> Radiotherapy administered after HBOT precludes radiation-induced damage to normal cells and augments the radiosensitivity of high-grade glioma cells.<sup>52,53</sup> The research findings of Kinoshita et al.<sup>54</sup> The researchers reported that the most appropriate time to carry out radiation therapy promptly following the course of oxygen therapy is within the initial 15 minutes after oxygen therapy.

The Columbia-Preston Medical Center carried out a radiotherapy trial for glioblastoma. Eighty patients who had not been treated previously and were pathologically verified as having glioblastoma were assessed; 38 patients underwent radiotherapy under hyperbaric oxygen, and 42 patients (the control group) received radiotherapy in ambient air. After 18 months, the survival rate of the oxygen group was markedly greater than that of the control group (28% vs. 10%). At the end of 36 months, no patients in the control group were alive, whereas 2 patients in the oxygen group remained alive after 45 months and 48 months. The median survival time of the oxygen treatment group was 38 weeks, whereas that of the ambient air control group was 31 weeks.<sup>55</sup>

Kohshi et al.<sup>22</sup> reported that computed tomography or magnetic resonance imaging (MRI) of 29 patients with malignant glioma indicated postoperative residual tumors. Fifteen patients received radiotherapy daily after HBO, and for 11 and 4 patients, the times from decompression to radiotherapy were 15 and 30 minutes, respectively. Another 14 patients did not undergo HBOT. In the HBOT group, 11 out of 15 patients (73%) exhibited a tumor reduction of  $\geq 50\%$ . All responders received radiotherapy within 15 minutes after decompression. In the non-HBOT group, 4 out of 14 patients (29%) demonstrated tumor reduction. The median survival times of patients who received and did not receive HBOT were 24 and 12 months, respectively, which were significantly different ( $P < 0.05$ ). No severe side effects were observed in HBOT patients.

Japanese scholars presented the interim outcomes of postoperative adjuvant therapy for high-grade gliomas. Forty-one patients underwent conventional fractionated radiotherapy with a total dose of 60 Gy. The chemotherapy included procarbazine, nimustine, and vincristine and was implemented during and after radiotherapy. Fifty-seven percent of the patients achieved a response, the average time to progression was 12.3 months, and the overall survival time was 17.3 months.<sup>56</sup> With the prolongation of the follow-up time, the results were subsequently updated. A total of 57 patients (39 glioblastoma patients and 18 grade III glioma patients) were included in the study. All 57 patients were capable of completing a total radiotherapy dose of 60 Gy immediately following one session of concurrent chemotherapy. The median overall survival time of all 57 patients was 20.2 months, the median survival time for 39 glioblastoma patients was 17.2 months, and the median survival time for 18 grade III glioma patients was 113.4 months.<sup>27</sup>

Kohshi et al.<sup>57</sup> also examined gamma-fractionated stereotactic radiotherapy in 25 patients with recurrent high-grade gliomas who had previously undergone chemotherapy and radiotherapy, including 14 patients with anaplastic astrocytoma and 11 patients with glioblastoma multiforme. The median survival time following fractionated stereotactic radiotherapy was 19 months for anaplastic astrocytoma patients and 11 months for glioblastoma multiforme patients. Among them, 4 patients exhibited a radiation effect with no viable cells, and their survival durations were between 50 and 78 months.

Italian scholars presented their interim research findings in a study on patients with recurrent high-grade glioma. In their hypofractionated stereotactic radiotherapy for nine patients with recurrent high-

grade brain glioma, hypofractionated stereotactic radiotherapy was continuously administered at a daily dose of 5 Gy for 3–5 days. Each dose was provided within 1 hour after HBOT. The disease control rate 3 months after hyperbaric oxygen radiotherapy was 55.5%. The median progression-free survival for all patients was 5.2 months, while the progression-free survival rates at 3 and 6 months were 55.5% and 27.7%, respectively. The median overall survival following hyperbaric oxygen radiotherapy is 10.7 months.<sup>25</sup>

Hartford et al.<sup>49</sup> investigated 38 patients with brain metastases. Among these patients, 19 underwent HBOT before stereotactic radiosurgery (SRS), with a total of 25 brain metastases. The other 19 patients constituted the control group, with a total of 27 metastases. There was no significant difference between the HBOT patients and the control patients in terms of radiation necrosis (RN)-free survival, whole-brain radiotherapy before RN-free survival, local recurrence-free survival before whole-brain radiotherapy for local recurrence, distant recurrence-free survival before whole-brain radiotherapy for distant recurrence, or overall survival. However, the 1-year estimated survival rate tended toward SRS combined with HBOT. Incorporating HBOT into SRS for brain metastases is feasible, and there is no evidence of a marked reduction in RN or other clinical outcomes.

## Cerebral Protective Role of Hyperbaric Oxygen Therapy in Glioma and Brain Metastases

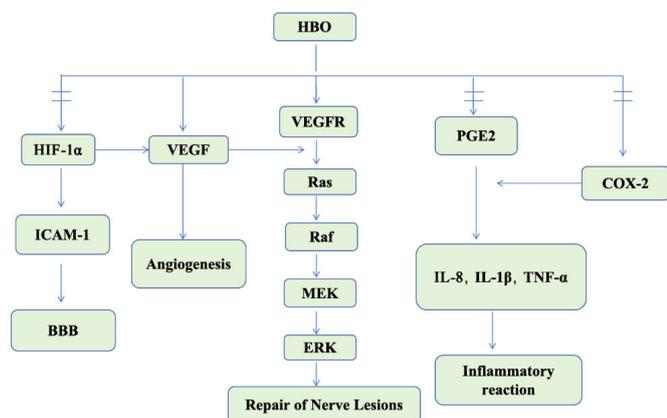
The immediate adverse reactions to radiotherapy for brain tumors include elevated intracranial pressure, fatigue, and delayed responses.<sup>58</sup> The long-term sequelae are RN and cognitive impairment, which typically occur 3–12 months after radiotherapy.<sup>59,60</sup> With the development of stereotactic radiotherapy for the treatment of brain tumors, the occurrence rate of radiation-induced brain necrosis is also increasing.<sup>59</sup> The occurrence rate of radiation-induced brain necrosis is to a certain extent a function of the dose. In a study comparing low-dose and high-dose radiation in the treatment of low-grade gliomas, the occurrence rates of grade 3–5 radiation toxicities, including RN, were 2.5% at 5040 cGy and 5% at 6480 cGy.<sup>61</sup>

The mechanism of radiation-induced brain necrosis may involve vascular alterations resulting from endothelial damage and the actions of proinflammatory cytokines, including vascular endothelial growth factor (VEGF), hypoxia-inducible factor 1, and tumor necrosis factor- $\alpha$ .<sup>62</sup> Vascular injury initiates the necrotic process. Damage to vascular endothelial cells results in fibrinoid necrosis of small arteries. This may give rise to focal coagulative necrosis as well as oligodendrocyte damage and demyelination.<sup>63</sup> Some researchers have assessed 11 pathological samples of RNs by employing anti-VEGF antibodies and anti-hypoxia-inducible factor-1 $\alpha$  antibodies. VEGF was not detected in the necrotic tissue. In the perinutrotic region, astrocytes were observed to be positive for VEGF expression. This might stimulate endothelial cell proliferation in necrotic tissue and necrotic tissue. Hypoxia-inducible factor-1 $\alpha$  was also detected in the periumcrotic tissue but was expressed at lower levels in the necrotic tissue. This suggests that the management of RN should be more focused on the periacrotic tissue rather than the necrosis itself.<sup>64</sup>

HBOT increases the generation of VEGF while supporting the milieu for new vascular growth. Supplying oxygen to underperfused tissues stimulates angiogenesis, thus preventing further hypoxic tissue necrosis.<sup>65</sup> Research has indicated that, via the VEGF/extracellular signal-regulated kinase signaling pathway, the application of HBOT can potentiate VEGF and upregulate its receptors vascular endothelial growth factor receptor-2, rat sarcoma viral oncogene homolog 1 (Raf-1), mitogen-activated protein kinase 1/2, and extracellular signal-regulated kinase.<sup>66</sup>

HBOT possesses anti-inflammatory characteristics in the brain by obstructing the release of proinflammatory cytokines. Research has demonstrated that HBOT can restrain the synthesis of prostaglandin E<sub>2</sub>, cyclooxygenase-2, and mitogen-activated protein kinase and decrease the expression of interleukin-8, interleukin-1 $\beta$ , and tumor necrosis factor- $\alpha$ .<sup>67-70</sup>

HBOT may suppress the hypoxia-inducible factor-1 $\alpha$  cascade and upregulate angiopoietin genes, thereby mitigating inflammation and facilitating angiogenesis.<sup>67,71</sup> Hypoxia resulting from radiation damage in astrocytes leads to an increase in hypoxia-inducible factor-1 $\alpha$ .<sup>65</sup> Hypoxia-inducible factor-1 $\alpha$  disrupts intercellular adhesion molecule-1, thereby compromising the integrity of the blood-brain barrier.<sup>72,73</sup> The biological mechanisms by which hyperbaric oxygen promotes the healing of radiation-induced brain injury are shown in **Figure 3**.



**Figure 3 | Biological mechanisms by which HBO facilitates the healing of radiation-induced brain injury.**

HBOT therapy inhibits HIF-1 $\alpha$ , reduces the disruption of ICAM-1, and maintains the integrity of the BBB. HBO therapy can also suppress the synthesis of PGE<sub>2</sub> and COX-2 mRNAs and decrease the levels of IL-8, IL-1 $\beta$ , and TNF- $\alpha$ , thereby alleviating the inflammatory response. Moreover, HBO therapy increases the production of VEGF and activates the Ras-Raf-MEK-ERK signaling pathway to repair nerve injuries. BBB: Blood-brain barrier; COX-2: cyclooxygenase-2; ERK: extracellular signal-regulated kinase; HBO: hyperbaric oxygen therapy; HIF-1 $\alpha$ : hypoxia-inducible factor-1 $\alpha$ ; ICAM-1: intercellular adhesion molecule-1; IL-1 $\beta$ : interleukin-1 $\beta$ ; IL-8: interleukin-8; MEK: mitogen-activated protein kinase; PGE<sub>2</sub>: prostaglandin E<sub>2</sub>; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ ; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.

Rascón-Ramírez et al.<sup>74</sup> reported a case of an RN that recurred following the partial resection of a malignant astrocytoma. The patient underwent SRS treatment with a total dose of 60 Gy. RN was managed via corticosteroid treatment and surgical resection of the lesion. At 38 months after SRS, the RN had recurred for the fourth time. The patient declined surgery; hence, HBOT was performed, the symptoms were alleviated, and there was no recurrence.

Smith and Fenderson<sup>75</sup> reported a 43-year-old male who was diagnosed with malignant astrocytoma, underwent total resection of the lesion, and then received radiotherapy with a total dose of 5490 cGy, accompanied by oral temozolomide chemotherapy. The follow-up MR image revealed that the RN was present. After various treatment options were offered, HBOT was selected. The patient received 60 sessions of 2 ATA HBOT, and the MRI demonstrated a marked reduction in white matter T<sub>2</sub> hyperintensity and edema, while the symptoms improved.

A patient with triple-negative breast cancer who developed brain metastatic lesions following receipt of standard chemotherapy and radiotherapy underwent stereotactic radiotherapy. Two months later, the patient exhibited worsening clinical symptoms, and MRI revealed that RN was accompanied by significant peritumoral edema. The patient responded inadequately to mannitol and corticosteroids. After being diagnosed with brain necrosis, short-term HBOT commenced, and intravenous Endostar was administered for a total of four cycles. The patient responded favorably to this strategy, with rapid and conspicuous improvements in MRI results and clinical symptoms. No tumor progression was observed 10 months after treatment.<sup>76</sup>

A retrospective analysis was performed on 78 patients who had a total of 101 brain metastases and received SRS treatment. Among them, 32 patients (with a total of 47 brain metastases) received prophylactic HBOT, and another 46 patients (with a total of 54 brain metastases) did not receive HBOT. On the basis of the imaging results, radiation-induced brain injuries were classified into two categories, namely, white matter injury (WMI) and RN. Radiation-induced brain injuries occurred in 5 lesions (11%) in the HBOT group (2 WMIs and 3 RNs) and 11 lesions (20%) in the non-HBOT group (9 WMIs and 2 RNs). The occurrence frequency of WMIs in the HBOT group was lower than that in the non-HBOT group ( $P = 0.05$ ). Prophylactic hyperbaric oxygen may have potential value for radiation-induced WMIs.<sup>77</sup>

At present, the results of the two ongoing prospective studies on HBOT for cerebral RN have not yet been reported. One study concerns the treatment of cerebral RN with HBOT combined with corticosteroids rather than with corticosteroid monotherapy (NCT00087815). Another study focused on the clinical improvement of patients with cerebral RN following gamma knife surgery treated with HBOT (NCT02714465).

## Hyperbaric Oxygen Recovers Nerve Injury and Restorates Motor Function in Gliomas and Brain Metastases

As the brain tumor progresses and compresses adjacent normal tissues, patients exhibit symptoms of neurological function impairment and motor dysfunction, specifically limb hemiplegia, paralysis, muscle atrophy, limb sensory impairment, language dysfunction, and depression.<sup>78-80</sup> After treatment, when the tumor is brought under control, most patients with symptoms of motor weakness remain stable or show improvement, while a small portion of patients have less desirable outcomes.<sup>81</sup>

HBOT can increase the expression of humanin, a small mitochondria-derived peptide that possesses neuroprotective properties and is capable of resisting various kinds of cellular damage.<sup>82</sup> With respect to mitochondrial research, neurons can release and transfer damaged mitochondria to glial cells for processing and recycling, and glial cells can release functional mitochondria into neurons. HBOT promotes the intercellular transfer of mitochondria from astrocytes to neurons, thereby achieving the ability to reverse neuroinflammation.<sup>83-85</sup>

Research indicates that HBOT facilitates the proliferation of neural stem cells and that neural stem cells additionally migrate to the lesion site.<sup>66</sup> Following HBOT, bone marrow stem cells likewise migrate to the ischemic region. The trophic factors secreted by these cells can once more facilitate nerve regeneration and restore cerebral health.<sup>86,87</sup>

Two studies have demonstrated that HBOT in combination with mesenchymal stem cells can facilitate the regeneration of peripheral nerves and the restoration of spinal cord injuries.<sup>88,89</sup> HBOT can

also facilitate the proliferation of skeletal muscle satellite cells and the maturation of muscle fibers, which is beneficial for muscle regeneration.<sup>90,91</sup> Intermittent hyperbaric exposure during exercise training enhances endurance performance by augmenting oxidative and glycolytic capabilities and upregulating proteins associated with mitochondrial biosynthesis in striated muscle.<sup>92</sup> These effects promote the rehabilitation of patients' motor function.

HBOT increases the oxygen content in the blood and may be conducive to treating ligament and muscle injuries resulting from hypoxia during exercise as well as alleviating muscle fatigue induced by plantar flexion exercise.<sup>93,94</sup> Research has indicated that HBOT can alleviate muscle soreness caused by eccentric contraction of the quadriceps femoris and damage caused by eccentric contraction of the peroneus longus.<sup>95</sup> Nevertheless, it has no recuperative effect on muscle soreness caused by eccentric contraction of the elbow flexors and knee flexors.<sup>96-98</sup>

We reported a case of a patient with recurrent glioblastoma who underwent HBOT immediately followed by hypofractionated SRS, with grip strength, isokinetic muscle strength testing, and gait analysis as the observational indicators. The evaluations before and after treatment revealed that, compared with those before treatment, the grip strength, isokinetic muscle strength, and gait parameters improved. It offers a promising alternative solution for dealing with muscle weakness and motor ability problems in the recurrence of glioblastoma.<sup>99</sup>

## Adverse Reactions of Hyperbaric Oxygen Therapy

HBOT treats patients by applying pressure and providing oxygen in an enclosed space. The common adverse reactions are ear/sinus barotrauma, claustrophobic anxiety, hypoglycemia, oxygen toxicity, pneumothorax, seizures, and dyspnea.<sup>100-103</sup> A retrospective study was carried out at the outpatient wound care center managed in Jacksonville (a city in the USA). Among the 1.5 million treatments analyzed, the proportion associated with adverse events was 0.68%. Ear barotrauma and restrictive anxiety were the most frequently reported events. Severe events are extremely rare, with less than 0.05 instances of oxygen toxicity per 1000 treatments, and there is only one confirmed case of pneumothorax.<sup>104</sup>

A retrospective analysis of 2334 patients treated at Assaf Harofeh Hospital in Israel revealed that 406 (17.4%) experienced adverse events (one or more) during HBOT. The overall incidence rate per 100,000 events:sessions was 721:100,000 (0.72%). The principal complication was middle ear barotrauma, which occurred in 16% of the patients and 0.04% of the sessions. Females and children under 16 years of age had a greater risk of barotrauma. Other complications, such as hypoglycemia, oxygen toxicity, dizziness, anxiety reactions, dyspnea, and chest pain, had an incidence ranging from 0.5–1.5% in patients.<sup>105</sup>

One study reported three cases of pulmonary edema related to HBOT. All three patients had cardiac disease and a decreased left ventricular ejection fraction. HBOT may alter the cardiac output between the right and left heart, give rise to bradycardia with left ventricular dysfunction, resulting in pulmonary edema. Researchers have recommended caution when employing HBOT in patients with heart failure or a decreased ventricular ejection fraction.<sup>106</sup>

HBOT may cause oxygen toxicity in the central nervous system, leading to seizures.<sup>107</sup> Hyperbaric oxygen-induced seizures are categorized as brief generalized tonic-clonic seizures. Although this is regarded as not causing residual cognitive impairment, it may have transient yet negative consequences for cognitive function and behavioral patterns.<sup>108</sup>

HBOT elevates intraocular pressure, and ocular structures may also be influenced and injured.<sup>109</sup> Hyperoxic myopia, cataracts, and lenticular ectopic fibrosis are ocular complications related to HBOT.<sup>109,110</sup> Other less frequently observed ophthalmic complications include cataracts, corneal ectasia, or retinopathy of prematurity.<sup>111</sup>

HBOT can modify glucose metabolism by affecting residual insulin secretion in diabetic patients and augmenting the brain's utilization of glucose. These alterations may ultimately result in hypoglycemia during the treatment course.<sup>112</sup> Although rare in nondiabetic patients, they may also suffer from hypoglycemia during HBOT. Researchers suggest evaluating their blood glucose levels before HBOT, as it may exacerbate their hypoglycemic conditions.<sup>101</sup>

## Conclusions

This review focuses on hyperbaric oxygen combined with radiotherapy for the treatment of gliomas and brain metastases. It expounds on the features of HBOT. Hyperbaric oxygen can ameliorate the hypoxic state of tumor cells and increase their radiosensitivity. With respect to treatment efficacy, hyperbaric oxygen combined therapy can improve the overall survival time of patients with gliomas. In cases of brain metastases, the combination of HBOT and SRS is practicable and presents certain advantages. Hyperbaric oxygen has a protective effect on radiation-induced brain injury and is beneficial for the recovery of neurological and motor functions. HBOT has multiple adverse effects, and special-group patients need to be cautious when it is used.

Although hyperbaric oxygen combined with radiotherapy has shown promising results in research, there is a relative scarcity of clinical studies. Moreover, the absence of multicenter prospective phase III clinical trials has led to limited clinical application. Another key limitation of this narrative review is the lack of sufficient long-term follow-up data on patients who received the combined treatment. This results in the inability to evaluate the durability of the tumor control effect, the likelihood of late-onset adverse reactions, and the long-term impact on patients' quality of life.

Future research should further explore the treatment mechanisms of hyperbaric oxygen combined with radiotherapy to develop personalized treatment regimens, optimize protective measures against radiation-induced brain injury, and improve patients' quality of life. Moreover, it is necessary to strengthen the prevention of adverse reactions, especially for special-population patients. Multidisciplinary cross-research should be carried out, more clinical studies should be conducted to verify the efficacy and safety, and doctor training should be strengthened to promote wide clinical application.

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