ORIGINAL ARTICLE

Hyperbaric Oxygen for Radiation Necrosis of the Brain

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ABSTRACT: ***Introduction:*** Hyperbaric oxygen therapy (HBOT) shows promising results in treating radionecrosis (RN) but there is limited evidence for its use in brain RN. The purpose of this study is to report the outcomes of using HBOT for symptomatic brain RN at a single institution. ***Methods:*** This was a retrospective review of patients with symptomatic brain RN between 2008 and 2018 and was treated with HBOT. Demographic data, steroid use, clinical response, radiologic response and toxicities were collected. The index time for analysis was the first day of HBOT. The primary endpoint was clinical improvement of a presenting symptom, including steroid dose reduction. ***Results:*** Thirteen patients who received HBOT for symptomatic RN were included. The median time from last brain radiation therapy to presenting symptoms of brain RN was 6 months. Twelve patients (92%) had clinical improvement with median time to symptom improvement of 33 days (range 1–109 days). One patient had transient improvement after HBOT but had recurrent symptomatic RN at 12 months. Of the eight patients with evaluable follow-up MRI, four patients had radiological improvement while four had stable necrosis appearance. Two patients had subsequent deterioration in MRI appearances, one each in the background of initial radiologic improvement and stability. Median survival was 15 months with median follow-up of 10 months. Seven patients reported side effects attributable to HBOT (54%), four of which were otologic in origin. ***Conclusions:*** HBOT is a safe and effective treatment for brain RN. HBOT showed clinical and radiologic improvement or stability in most patients. Prospective studies to further evaluate the effectiveness and side effects of HBOT are needed.

RÉSUMÉ: Utilisation de l'oxygénothérapie hyperbare à la suite de séances de radiothérapie entraînant la mort du tissu cérébral. ***Introduction:*** Si l'oxygénothérapie hyperbare (OHB) laisse entrevoir des résultats prometteurs dans le traitement des radionécroses (RN), les preuves demeurent limitées quant à son utilisation dans le cas de RN du cerveau. L'objectif de cette étude est de présenter des résultats de recherche liés, dans un seul établissement de santé, à l'utilisation de l'OHB dans le cas de RN symptomatiques du cerveau. ***Méthodes:*** Pour ce faire, nous avons effectué une analyse rétrospective des dossiers de patients atteints de RN symptomatiques du cerveau entre 2008 et 2018 et ayant été traités lors de séances d'OHB. Nous avons aussi recueilli des données de nature démographique et d'autres portant sur l'utilisation de stéroïdes, sur la réponse clinique et radiologique des patients et sur les toxicités. Le point de départ (*index time*) de notre étude a été la première séance d'OHB alors que son principal indicateur de résultat a été l'amélioration sur le plan clinique d'un symptôme particulier, ce qui a inclus une réduction des doses de stéroïdes. ***Résultats:*** Au total, treize patients atteints de RN symptomatiques ont été inclus dans cette étude. Le temps médian entre une ultime séance de radiothérapie et l'apparition de symptômes de RN a été de 6 mois. Douze patients (92 %) ont donné à voir une amélioration de leur état médical, la période médiane d'amélioration de leurs symptômes étant de 33 jours (étendue : 1–109 jours). On a observé chez un seul patient une amélioration transitoire à la suite de séances d'OHB, les symptômes de RN étant réapparus au douzième mois. Sur les huit patients ayant subi un examen d'imagerie de suivi, quatre d'entre eux ont montré des signes d'amélioration sur le plan radiologique tandis que quatre autres ont donné à voir une RN stable. Fait à noter, deux patients chez qui l'on avait observé une amélioration radiologique initiale ou une stabilité de leur état ont montré une détérioration ultérieure à la suite d'un examen d'IRM. Le taux de survie médian de ces patients et leur suivi médian ont été respectivement de 15 mois et de 10 mois. Enfin, sept d'entre eux ont signalé des effets secondaires attribuables à l'OHB, dont quatre d'origine otologique. ***Conclusions:*** L'OHB demeure un traitement efficace et sécuritaire dans le cas des RN du cerveau. Elle a permis d'observer chez la plupart des patients une amélioration clinique et radiologique ou à tout le moins une stabilité de leurs symptômes. Cela dit, des études prospectives sont nécessaires afin de pouvoir évaluer plus en profondeur son efficacité et ses effets secondaires.

Keywords: Abnormalities, Radiation-induced, Brain neoplasms, Hyperbaric oxygenation, Necrosis

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Introduction

Radiation therapy (RT) is a safe and effective treatment for central nervous system tumours in both paediatric and adult patients.[1–3] Radiation necrosis of treated tissues can develop as an unintended complication of RT, which can affect patients' performance status or quality of life. The incidence of brain radionecrosis (RN) ranges from 2.5% to 24% of treated patients, depending on diagnostic criteria used.[4] Radiation necrosis is more common after re-irradiation of brain tissues.[5] Clinical manifestations of brain RN vary according to location but can include focal neurologic deficits or seizures, and the severity can range from an asymptomatic imaging finding to severe brain oedema causing death.

There are many treatments available for brain RN, but there is no clear standard of care. Patients who are asymptomatic can be observed, while those who are symptomatic are managed with corticosteroids, hyperbaric oxygen therapy (HBOT), bevacizumab, pentoxifylline, vitamin E, laser-induced thermal therapy and/or surgery.[6–10] A recent Cochrane systematic review showed paucity of data on the topic, and was only able to include three comparative studies that used bevacizumab, edaravone and vitamin E.[11] HBOT is a non-invasive treatment that may stabilise necrosis, promote tissue repair and expedite neurological recovery.[12,13] Small retrospective studies have demonstrated high rates of benefit with either rates of stability or improvement estimated at 70%–80% of treated patients.[12,14–18]

Due to the sparsity of data on the use of HBOT for brain RN, this study aimed to review our institutional experience with HBOT and evaluate the efficacy of this treatment in stabilising or improving clinical symptoms and radiologic appearance of brain RN.

Methods

This was a retrospective cohort study. We included 13 adult patients diagnosed with symptomatic brain RN and who underwent HBOT at Toronto General Hospital between 2008 and 2018. Patients were permitted to have received single or multiple courses of RT, including stereotactic radiosurgery (SRS). Patients who had previous HBOT for an indication other than brain RN were excluded. The diagnosis of symptomatic RN based on the patient's history, physical examination and concordant magnetic resonance imaging (MRI) findings was independently confirmed by the treating radiation oncologist, neuroradiologist and hyperbaric medicine physician. Establishing this diagnosis is important because only patients who have a "delayed radiation injury (soft tissue [or] bony necrosis)" are eligible for funding by provincial health insurance; all patients met this criterion for public insurance funding.[19,20] Demographic data, primary diagnosis and previous oncologic treatment, symptoms and diagnosis of brain RN, HBOT dose and administration, toxicities, radiologic and clinical outcomes were extracted. HBOT was administered at the Hyperbaric Medicine Unit at Toronto General Hospital using 2.0–2.4 atmospheric absolute (ATA) at 14.7–20 psi for 90 minutes daily. The number of daily dives given was at the discretion of treating physician; the median dive number was 30 (range 20–60). Post-treatment MRI studies were available in eight patients, which included three-dimensional gadolinium-enhanced T1 as well as T2 fluid attenuated inversion recovery (FLAIR) sequences. Magnetic resonance spectroscopy was not routinely performed.

The primary endpoint of the study was clinical improvement of a presenting symptom after initiation of HBOT which included a decrease in corticosteroid dose. RN was retrospectively graded using the Common Toxicity Criteria for Adverse Events version 5.0, using the "Central nervous system necrosis" subscale, as follows: Grade 1 – Asymptomatic, clinical or diagnostic observations only; Grade 2 – Moderate symptoms, corticosteroids indicated; Grade 3 – Severe symptoms, medical intervention indicated; Grade 4 – Life-threatening consequences, urgent intervention indicated; Grade 5 – Death. Specifically, those requiring inpatient hospitalisation were assigned grade 3 or greater.[21]

Radiologic improvement was determined using brain MRI and defined as a decrease in lesion enhancement intensity (by neuroradiologist determination) or lesion size (on enhanced T1 sequences) and/or brain oedema (on FLAIR sequences). Clinical characteristics were reported descriptively. Vital status and date of death of patients were collected through the medical chart; those who were lost to follow-up were found through publicly accessible records (i.e. obituaries). Overall survival was calculated from the first day of HBOT to date of death using the Kaplan–Meier method; those still alive or lost to follow-up were censored. Time to first clinically apparent necrosis improvement was counted from the first day of HBOT. Analyses were performed using SPSS v23.0 (IBM, IL, USA). The study was approved by the research ethics board of University Health Network.

Results

Thirteen patients had a diagnosis of brain RN and were treated with HBOT (Table 1; the complete version is available as Supplementary Table 1). The median age was 46 years (range 21–63 years); 39% were male. The initial oncologic diagnoses that required radiotherapy were brain metastasis (6; 47%), ependymoma (2; 15%), nasopharyngeal carcinoma (NPC, 2; 15%), medulloblastoma (1; 8%), meningioma (1; 8%) and cavernoma (1; 8%). Four patients received focal brain RT, two had received intensity modulated radiotherapy (IMRT) for nasopharyngeal cancer with exposure of brain tissue to high RT doses, two had SRS, three underwent whole brain radiotherapy (WBRT), one had craniospinal irradiation (CSI) upfront and one had missing radiotherapy details. Among these, eight had repeat brain RT with fractionated focal brain RT (3), accelerated fractionation focal IMRT for nasopharyngeal cancer (1) and SRS (2), WBRT (1) and CSI (1). All patients had previously underwent craniotomy as part of the course of their primary treatment except for four patients with cavernoma ($n = 1$), brain metastasis ($n = 1$) and NPC ($n = 2$), the latter received definitive chemoradiotherapy. Seven and four patients received chemotherapy and targeted therapy as part of their primary oncologic treatment, respectively.

The median time from last brain RT to presenting symptoms of brain RN was 6 months (range 1–351 months). Common presenting symptoms were hemiparesis, vision change and balance/gait issues followed by hearing change, alteration in sensorium, swallowing problems, dysarthria, diplopia, cognitive issues, seizures and headache. All of the patients were diagnosed radiologically and none underwent biopsy or resection of presumed brain RN. Available imaging was retrospectively re-reviewed; of 12 patients with available MRI source data, 11 (92%) patients had enhancement of the necrotic lesion and 11 (92%) had oedema seen on T2 FLAIR sequences. One patient

Table 1: Listing of cases. Some patients' grade of toxicity were not assessable, but the medical chart documented clear clinical improvement.

Patient	Age/ Sex	Primary Oncologic Disease	Cranial RT		Onset of symptom from last RT (months)	Location of necrosis	Enhance-ment on MRI	Edema on MRI	Steroid Use before HBOT	CTCAE Pre HBOT	HBOT treatment		CTCAE Post HBOT			Clinical improvement	Radiologic improvement			Toxicities	Vital Status	Time from start to HBOT to last follow up or death (months)
			RT 1	RT 2							Atm pressure	Dives	3 mo	6 mo	12mo		3 mo	6mo	12mo			
1	41/M	Brain metastasis	WBRT 30/10	GK 24	1	Right basal ganglia	Yes	Yes	Yes	3	2.4 ATA x 90 mins, 20 psi	20*	2	–	–	Yes	Worse #	Yes	–	None	Died	15
2	63/F	Brain metastasis	WBRT 30/5	Focal boost	13	Left optic nerve	–	–	No	3	2.4 ATA x 90 mins, 20 psi	30	1	1	1	Yes	–	–	–	Barotrauma, left ear effusion	Alive	1
3	32/F	Ependymoma grade 2	Focal RT 59.4/33	Focal RT 54/30	2	Right cerebellar peduncle, pons, cerebellar hemisphere	Yes	Yes	Yes	3	2.4 ATA x 90 mins, 20 psi	30	–	–	–	Yes	–	Yes	Stable	None	Died	24
4	46/F	Brain metastasis	No data	No data	3	Right medial rolandic area	Yes	No	–	–	2.4 ATA X 90 mins 20 psi	30	2	2	–	Yes	–	–	–	Barotrauma both ears	Alive	47
5	46/M	Recurrent meningioma	Focal RT 50/25	Focal RT 50/25	4	Left frontal parasagittal area	Yes	Yes	Yes	3	2.4 ATA x 90 mins 20 psi	30*	2	2	–	Yes	Stable	Stable	Worse	shortness of breath (after attempted 2nd course of HBOT)	Alive	17
6	39/F	Brain metastasis	GK 15	WBRT 30/10	6	Left middle cerebellar peduncle and left pons	Yes	Yes	Yes	4	2.4 ATA x 90 mins 20 psi	30	3	–	–	Yes	Stable	–	–	None	Died	10
7	21/F	Brain metastasis	Focal RT 35/5	–	6	Right and left frontal lobes	Yes	Yes	Yes	–	2.0 ATA x 90 mins 14.7 psi	20	–	–	–	No (required surgery)	–	–	–	Otalgia	Alive	60
8	49/M	Cerebellar cavernoma	Linac SRS 16	–	5	Right cerebellar peduncle and pons	Yes	Yes	–	4	2.0 ATA x 90 mins 14.7 psi	30	3	3	3	Yes	–	Yes	–	Left tympanostomy tube, right TM perforation	Died	10
9	56/M	Brain metastasis	WBRT 30/10	GK 18, 21	3	Left occipital area	Yes	Yes	Yes	4	2.0 ATA x 90 mins 14.7 psi	30	2	–	–	Yes	Stable #	–	–	Mild blurring of vision	Died	4
10	30/F	Recurrent ependymoma	Focal RT 60/30	CSI 36/20 Focal boost 18/10	6	Right temporal, parietal and occipital lobe	Yes	Yes	Yes	4	–	–	2	2	4	Yes	Yes	Stable	Worse	–	Alive	12
11	50/F	Medulloblastoma	CSI36/18PF boost 16/8	–	348	Abducens nerve	No**	Yes	No	2	2.4 ATA x 90 mins 20 psi	60	1	1	–	Yes	–	–	Stable	None	Alive	10
12	63/F	Nasopharyngeal cancer	IMRT 70/35	IMRT 50.6/46 bid	16	Base skull, temporal and lower parietal lobes	Yes	Yes	Yes	2	2.4 ATA x 90 mins 20 psi	30	1	–	–	Yes	–	–	–	None	Alive	2
13	57/M	Nasopharyngeal cancer	IMRT 70/35	–	62	Right temporal lobe	Yes	Yes***	No	2	2.4 ATA x 90 mins 20 psi	28	0	–	–	Yes	–	–	–	Mild blurring of vision	Alive	1

HBOT - hyperbaric oxygen therapy, WBRT - whole brain radiotherapy, GK - gamma knife stereotactic radiosurgery, RT - radiotherapy, SRS - stereotactic radiosurgery, PF boost - posterior fossa boost, TM - tympanic membrane

*prescribed course of HBOT not completed

**abducens nerve not well seen on MRI (T1 contrast-enhanced sequence was acquired with 4 mm slice thickness)

***observed on T2 sequence (FLAIR sequence not done because study was protocolled as a head-and-neck study)

#MRI done at the end of HBOT

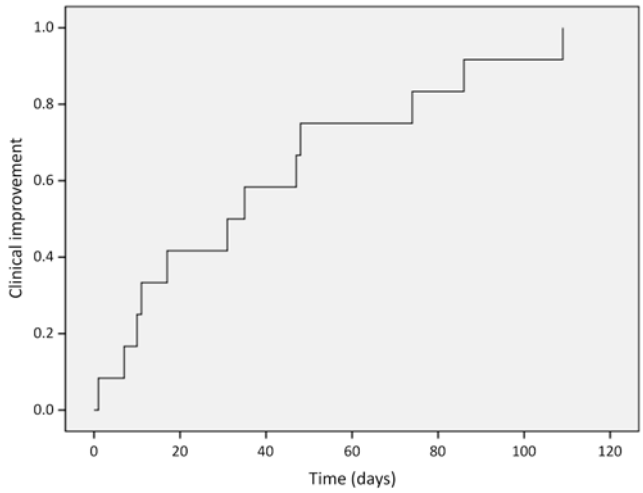

Figure 1: *Time to clinical improvement after initiation of HBOT.*

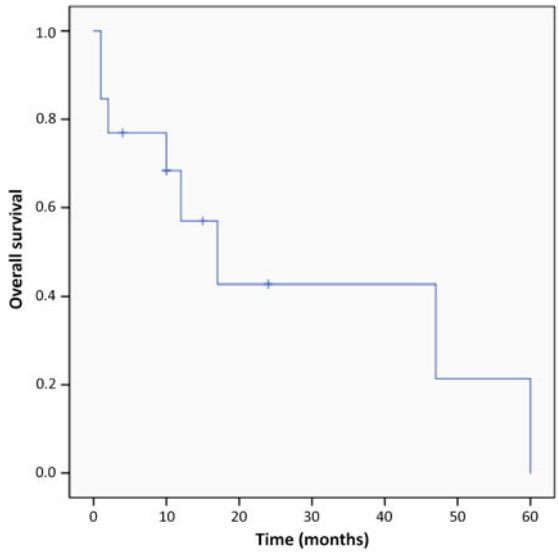

Figure 2: *Overall survival of all patients from the first day of HBOT.*

did not have MRI available because the patient was referred for HBOT from another province, while one patient had necrosis of the abducens nerve which was not well seen on diagnostic MRI. Dosimetric data were available for 10 patients; among patients who received SRS, the radiation plan's point maximum dose was 16.65 Gy, while in fractionated RT the cumulative, composite prescription was 120.6 Gy.

All patients underwent a single course of HBOT except for one who had a second course for recurrent RN. Six patients were treated between 2008 and 2011, while seven patients were treated between 2012 and 2018. The median time from presenting symptoms to start of HBOT was 4 months (range 0–11 months). Seven patients reported some treatment toxicity: mild barotrauma (2), ear effusion (1), otalgia (1), tympanic membrane perforation requiring tympanostomy tube insertion (1), transient, mild blurring of vision (2) and shortness of breath (1). All patients finished the prescribed course of HBOT except for two, which were discontinued due to uncertain benefit in one (patient 1) and dyspnea in the case of second course of HBOT (patient 5).

Twelve patients (92%) developed clinical improvement: eight during the course of HBOT and four within 1 month after HBOT completion (Figure 1), including the two patients who stopped HBOT. A single patient did not experience clinical improvement and required surgical intervention for RN (patient 7). The median time from initiation of HBOT to symptom improvement was 33 days (range 1–109 days). Among these 12 patients, 10 had evaluable necrosis toxicity grades pre-HBOT and post-HBOT; all had improvement by 3 months after HBOT. One patient had clinical initial improvement at 3 and 6 months, but worsened to grade 4 at 12 months; therefore, one patient did not have durable symptom improvement after HBOT (patient 5). Two more patients had documented clinical improvement but insufficient information to grade toxicity before and after HBOT. The medical records of 11 patients (85%) described steroid use prior to HBOT. Three were never started on steroids, five were using steroids throughout the HBOT and three were able to taper their steroid dose during treatment. The steroid use after HBOT was not available for review.

Eight patients had evaluable MRI at the end of or after HBOT; four patients had improved MR appearances, while the remaining four had stable necrosis appearance on MRI on follow-up. Two patients (patients 5 and 10) had deterioration in MRI appearances at 17 months after HBOT and 9 months from the start of HBOT, respectively, in the background of initial radiologic stability or improvement. Patient 1 had MRI after 20 dives which showed worse appearance of MRI; this led to discontinuation of HBOT and reinstitution of targeted therapy (erlotinib). Interestingly, the same patient had clinical improvement during HBOT with reduction in steroid dosage and had radiologic improvement after 6 months.

The overall median follow-up time from HBOT was 10 months (1–60 months). Eight patients were alive at last contact and five died (Figure 2); median survival was 15 months. The causes of death were tumour progression 17 months after HBOT (1; patient 3), complications of brain RN after transient improvement (2) and unclear aetiology (2; lost to follow-up). Patient 3's tumour recurrence was within the original tumour bed in the fourth ventricle, rather than within the right cerebellar peduncle (where the treated necrosis was located).

Discussion

This retrospective review presents the largest single institution experience on the use of HBOT for adult brain RN. Our series demonstrates that HBOT was helpful in stabilising or improving the symptoms of brain RN in most patients. Moreover, symptom improvement persisted in a majority of cases, except for one patient. Some patients did develop side effects from HBOT, though most were limited to otologic complications.

Tissue necrosis is a known infrequent side effect of radiotherapy that can occur in bones, soft tissues and brain.[22,23] HBOT has been used to treat air embolism, arterial insufficiencies, carbon monoxide poisoning, myonecrosis, compromised soft tissue grafts and flaps, crush injuries, decompression sickness, acute sensorineural hearing loss, intracranial abscess, necrotizing soft tissue infections, refractory osteomyelitis, severe anemia, thermal burns and delayed radiation injuries.[24] Small retrospective studies had previously reported the benefit of HBOT in treating brain RN. However, this is the largest known published series of adults treated with HBOT, which supports a clinical benefit of HBOT for this indication.

Table 2: Previous studies, published and unpublished, on use of hyperbaric oxygen for brain necrosis

Study	*n*	Initial steroid use	Clinical improvement or stability, *n* (%)	Radiologic improvement or stability, *n* (%)	Toxicity
Leber et al.[38]	2	No	–	2 (100)	None
Chuba et al.[12]+	10	Yes	10 (100)	9 (90)	Ear pain (1), sinusitis (1)
Kohshi et al.[17]	1	Yes	1 (100)*	1 (100)*	None
Cihan et al.[16]	1	Yes	1 (100)*	1 (100)*	None
Wanebo et al.[15]	1	Yes	1 (100)	1 (100)	Not reported
Alyahya et al.[46] (abstract)	6	Not reported	5 (83)	5 (83)	Not reported
Singh et al.[14] +(abstract)	39	Yes	29 (74)	29 (74)	Not reported
Aghajan et al.[18]+	5	Yes	5 (100)	4 (80)	Anxiety (1), tachycardia (1)^
Present study	13	8	12 (92)	8 (100)#	Mild barotrauma (2), Ear effusion (1), Tympanic membrane perforation (1), Blurring of vision (2), Lung toxicity (1)

*Had two courses of HBOT.
#Only 8 out of the 12 patients had evaluable MRI post-HBOT.
^Total population is seven patients which included brain tumours, the patients who had developed these toxicities were not specified.
+Included paediatric population.

Radiation Necrosis

Several mechanisms have been proposed for the development of brain RN. Release of vascular endothelial growth factor stimulated by endothelial cell damage triggers this pathologic process; these cascading events lead to microvascular permeability, oedema and necrosis.[25–27] Other possible mechanisms include astrocyte hyperplasia and hypertrophy, oligodendrocyte damage and demyelination or perturbation of the fibrinolytic pathway.[28–30] However, the mechanism of action of HBOT is not fully understood. HBOT has been used as a treatment for other radiation-induced injuries in various tissues.[31] It has been proposed that HBOT produces a positive oxygen gradient and subsequently promotes cellular and vascular repair.[32,33] In addition, previous animal studies have shown that HBOT decreases anaerobic conditions in the brain.[34] Adverse radiation effect can occur early on which is mainly due to oedema and is frequently relieved by a course of corticosteroids, but those patients with necrosis occurring after 6 months are typically brain RN and more difficult to treat.[35]

The incidence of brain RN ranges from 2.5% to 24% of treated patients, depending on diagnostic criteria used.[4] The variation may be due to improvement in RN diagnosis, awareness and length of oncologic follow-up.[36] Brain RN classically has a median time of onset of 6–12 months from last brain RT[12,14–18,37], though prolonged expression of injury can occur as long as 4 years after SRS.[38] RN is associated with dose–volume parameters, prior radiation treatment, concurrent chemotherapy, location, primary cancer histology, planning treatment volume and intrinsic idiopathic radiosensitivity.[36] Higher rates of RN can be seen in for patients receiving concurrent chemoradiation compared to radiation alone[37]; in our study, two patients received concurrent chemotherapy for NPC. In our cohort of patients, the median time to develop symptoms after brain RT was 6 months. Interestingly, one patient in the present study developed symptoms of brain RN 29 years after radiotherapy, likely due to an exacerbation of chronic tissue damage. Previous studies have shown that those who manifest symptoms early after brain RT have a better prognosis compared to those who become symptomatic late and are considered as a late radiation injury.[39] Thus, there may be a difference in the pathogenesis of early- and late-onset brain RN.

Diagnosis of brain RN is challenging because the location of the high-dose radiation area is also a frequent site of local disease progression, which is always on the differential diagnosis of symptoms or imaging findings. The time to develop RN with initial RT is usually similar to the time to develop tumour recurrence. Histopathology is the gold standard for diagnosis; however, in our cohort of patients, biopsy was not performed to confirm the diagnosis of brain RN due to the need to start empiric therapy or an inaccessible lesion location. Brain MRI can sometimes differentiate brain RN through the use of diffusion-weighted imaging (DWI) and spectroscopy, but was not consistently available for our study cohort.[40–42]

Treating Necrosis

The initial management of brain RN is observation for an asymptomatic patient, while steroids are given in symptomatic patients to allow for rapid symptom relief.[9] A previous case report described brain necrosis that symptomatically improved after steroid initiation but took 6 months to taper the dose.[43] Some studies use steroids as a comparator arm which gives insight on the effectiveness of steroids alone in brain RN. In a study investigating the role of edaravone, the control arm (steroids alone) was only able to provide improvement in 38.5% of patients after 3 months on the Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic criteria (LENT-SOMA) scale and on brain MRI.[44] Long-term use of steroids is associated with many complications and doses should be

decreased as soon as possible. Bevacizumab can also be given in RN due to its anti-angiogenesis properties. A small randomised control trial showed bevacizumab was able to reduce oedema, post-gadolinium contrast enhancing lesion size, and neurologic and clinical symptoms compared to a control group.[45]

In our cohort, a median of 30 HBOT dives were administered (range 20–60); this is consistent with prior reports, where the number of dives varied between 20 and 60 dives.[12,14–17,38,46] Our cohort showed that 92% of the patients improved: 61.5% responded clinically during the course of HBOT, while 30.5% responded within 1 month of HBOT. This is consistent with previous reports that some patients attain clinical response even during a course of HBOT.[17,38] Data from the present study support HBOT as a treatment option for radiation necrosis.

Selected studies from the literature are presented in Table 2; similar to our data, the proportion of patients who develop clinical and radiologic improvement or stability is high. Among these, three studies included both paediatric and young adults in their population. Two case reports even reported patients who had symptomatic recurrence after the course of HBOT; in these studies, the patients were given another course of HBOT which afforded relief.[16,17] In our cohort, one patient had received two courses of HBOT, but that patient was not able to complete the second course due to the development of dyspnea.

Our cohort included some patients who were treated initially with steroids and further improvement was seen with the addition of HBOT. We recognise that the effect of steroids may have contributed to the clinical and radiological improvement of this cohort and cannot be definitively isolated from the effect of HBOT. This practice is in concordance with typical clinical practice, wherein multiple modalities of treatments are instituted for brain RN. However, baseline status was determined at the initiation of HBOT; thus, improvements are more likely attributable to hyperbaric oxygen as opposed to steroids. In fact, all of the previous studies except one that evaluated HBOT for brain RN found that their patients were on steroids either before or during HBOT (Table 2).[12,14–18,38,46] Furthermore, the effect of HBOT may be effective against both the reversible and irreversible components of brain RN, but this retrospective study is not able to determine this difference. One of the limitations of the present study was that the steroid use after HBOT was unavailable for review.

Seven of the patients reported toxicities related to HBOT, although most of them were treatable. The most common was ear barotrauma, which can be prevented or treated with tympanostomy tubes. One patient (patient 5) had treatment-limiting toxicity (dyspnea), which necessitated discontinuation of a second course of HBOT. A study by Chuba et al. reported that HBOT was tolerable and resulted only in mild toxicity including ear pain requiring myringotomy and sinusitis.[12] Two studies reported two patients each and neither reports documented any toxicity from HBOT, even after repeated courses of treatment.[16,17]

HBOT costs 350 CAD (260 USD) per dive. A typical course of treatment of 20–30 dives would cost 7000–10,500 CAD. This might be viewed as costly burden to the healthcare system, but if effective, it may translate to healthcare savings because more costly surgical intervention and complications of prolonged steroids will be averted. Moreover, the cost of bevacizumab, another common therapy for RN, is 12,600 CAD per course (7.5 mg/kg intravenous every 4 weeks for four cycles)[45,47]; this amount does not include nursing or chemotherapy administration costs.

As of our knowledge, this retrospective review is the largest published series of patients investigates the use of HBOT in brain RN. This study does have limitations, however. Use of advanced MRI techniques was limited to standard enhanced T1 and FLAIR sequences; DWI was not always available and spectroscopy was not performed. Because histopathologic diagnosis was not obtained, tumour progression cannot be completely ruled out. This study is unable to compare the efficacy of HBOT as compared with bevacizumab. Varying tumour diagnoses and radiation treatments were included, which is a limitation inherent to retrospective outcomes research. The HBOT treatment protocol varied slightly between patients, typically ranging from 20 to 30 dives and 2.0 to 2.4 ATA; however, all treatments were delivered at a single hyperbaric facility, ensuring consistent treatment protocols and reporting. It would be ideal to measure the patient-reported quality of life outcomes after radiation necrosis and treatment with HBOT, ideally in a prospective manner. In such a study, there should be standardised reporting of clinical outcomes and toxicities of HBOT. We recognise the limited evidence on this topic; there is presently a phase 2, single-arm trial named Adverse Radiation Effects After Gamma Knife Radio Surgery and Hyperbaric Oxygen Therapy from Italian investigators which will expect to finish accrual in May 2019 (ClinicalTrials.gov identifier, NCT02714465). Bevacizumab is also emerging as an efficacious treatment for radiation necrosis; however, efforts to study this have been challenging. There is a multi-institutional, cooperative group study that is evaluating bevacizumab for radiation necrosis after SRS (ClinicalTrials.gov identifier, NCT02490878), though this study closed in late 2018 due to poor accrual.

Conclusions

HBOT renders favourable outcomes in the treatment of brain RN; HBOT led to clinical and radiologic improvement or stability in most patients. Many individuals were able to avoid or reduce their dose of corticosteroids during or after HBOT. HBOT can safely be administered with a tolerable toxicity profile, though otologic complications were common. Further study is required to a) prospectively evaluate HBOT as a treatment for radiation necrosis and b) compare its efficacy with other interventions such as bevacizumab.

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Conflict of Interest

NL has received an honorarium from Abbvie, outside the submitted work. Dr AWE is the medical director at Medical Oxygen Repair, a HBOT facility in Toronto, Canada. DST's institution received funds from Varian Medical Systems, Mevion Medical Systems, RayStation Laboratories, Hitachi, IBA and ProTom, outside the submitted work. The other authors have no conflict of interest to disclose.

Statement of Authorship

Conception and design – JC, RK and DT.
Data extraction – JC, MD and DT.
Synthesis and analysis – all authors.
Manuscript preparation and review and final approval – all authors.

Supplementary Material

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