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Original Article

Sensitizing brain metastases to stereotactic radiosurgery using hyperbaric oxygen: A proof-of-principle study

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ABSTRACT

Purpose: Increased oxygen levels may enhance the radiosensitivity of brain metastases treated with stereotactic radiosurgery (SRS). This project administered hyperbaric oxygen (HBO) prior to SRS to assess feasibility, safety, and response.
Methods: 38 patients were studied, 19 with 25 brain metastases treated with HBO prior to SRS, and 19 historical controls with 27 metastases, matched for histology, GPA, resection status, and lesion size. Outcomes included time from HBO to SRS, quality-of-life (QOL) measures, local control, distant (brain) metastases, radionecrosis, and overall survival.
Results: The average time from HBO chamber to SRS beam-on was 8.3 ± 1.7 minutes. Solicited adverse events (AEs) were comparable between HBO and control patients; no grade III or IV serious AEs were observed. Radionecrosis-free survival (RNFS), radionecrosis-free survival before whole-brain radiation therapy (WBRT) (RNBWFS), local recurrence-free survival before WBRT (LRBWFS), distant recurrence-free survival before WBRT (DRBWFS), and overall survival (OS) were not significantly different for HBO patients and controls on Kaplan-Meier analysis, though at 1-year estimated survival rates trended in favor of SRS + HBO: RNFS – 83% vs 60%; RNBWFS – 78% vs 60%; LRBWFS – 95% vs 78%; DRBWFS – 61% vs 57%; and OS – 73% vs 56%. Multivariate Cox models indicated no significant association between HBO treatment and hazards of RN, local or distant recurrence, or mortality; however, these did show statistically significant associations ($p < 0.05$) for: local recurrence with higher volume, radionecrosis with tumor resection, overall survival with resection, and overall survival with higher GPA.
Conclusion: Addition of HBO to SRS for brain metastases is feasible without evident decrement in radiation necrosis and other clinical outcomes.

Metastatic brain tumors are the most common central nervous system (CNS) tumors in adults [1]. Radiation therapy, along with surgery, is the standard of care for treating brain metastases [2]. Due to lower rates of neurotoxicities, stereotactic radiosurgery (SRS) is often preferred to whole brain radiation therapy (WBRT) [3,4]. However, a variety of factors affect the efficacy of SRS, such as target size, dose, and histology [5].

Tumor hypoxia confers radiotherapy resistance to metastases. This is a potential barrier to effective radiation treatment – particularly for larger lesions, in which lower levels of dissolved oxygen may be available for radical formation and consequent nuclear DNA damage. Preclinical and modeling studies suggest that tumor hypoxia may be particularly important in lowering SRS treatment efficacy due to lack of opportunity for re-oxygenation inherent with single-fraction treatment [6,7].

Hyperbaric oxygen (HBO) therapy, in which patients breathe 100% oxygen at a high ambient atmospheric pressure, may be an appealing strategy for overcoming tumor hypoxia. HBO dramatically increases delivery of dissolved oxygen to tissues, thereby potentially increasing the radiation sensitivity of hypoxic tumors with only minimal impact on radiosensitivity of already well-oxygenated surrounding structures [8,9]. However, several studies over the past several decades have found worsened rates of radiation tissue injury following HBO's combination with radiation therapy, discouraging this line of investigation [9].

To our knowledge, HBO has not been studied as a radiosensitizer for SRS in the treatment of brain lesions. In this Phase I,

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case-control trial, we hypothesized that administering HBO prior to SRS would be feasible, and that it would not result in increased rates of radionecrosis or other toxicities compared to a matched group of controls. We also hypothesized that addition of HBO would not worsen (but might potentially improve) rates of tumor control, survival, and quality of life.

Methods

Patient selection and treatment schema

Histologically-proven adult cancer patients with brain metastases under 5-cm diameter and Karnofsky Performance Status (KPS) over 60 without contraindications for HBO- or cranial SRS-treatments were eligible for enrollment. Participants received HBO at 100% oxygen and 2.4 atmospheres absolute (ATA) for 30 minutes, a dose that had yielded no additional toxicities in combination with definitive radiation therapy in a prior phase I head-and-neck cancer trial (conducted by some of the authors) [10]. Patients were transported from the hyperbaric chamber to the linear accelerator while receiving 100% oxygen through a non-rebreather face mask at 15 liters/minute. Per protocol, patients were required to undergo SRS within 15 minutes after exiting the hyperbaric chamber. All patients undergoing HBO treatment provided protocol-specific informed consent.

Radiosurgery targets were defined using gadolinium-enhanced thin-cut (1.5 mm) magnetic resonance imaging (MRI) scans performed within one week prior to SRS and fused with contrast-enhanced computed tomography (CT) scans obtained at simulation. PTVs typically included 1–2 mm of tissue beyond enhancing disease for intact lesions, while PTV margins were 2-3 mm beyond the resection cavity and residual enhancement for post-operative targets. SRS typically was delivered with the patient's head immobilized on a 6-DOF Varian TrueBeam™ couch, while on-board CBCT imaging was used for computer-assisted 6-degree-of-freedom alignment to CT-images acquired at simulation, and AlignRT® optical surface guidance was used for target stability during SRS delivery. Dose was prescribed to the PTV margin respective to target diameter: 20 Gy for $\leq$ 20 mm, 18 Gy for 21–30 mm, and 15 Gy for 31–40 mm, as well as 12 Gy for > 40 mm postoperative cavities [11,12].

Patients were followed-up four to six weeks after HBO and SRS treatment and every-three months thereafter, including history and physical examinations, magnetic resonance imaging (MRI) scans, and quality of life (QOL) questionnaires. QOL assessments included the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLC-C30), the EORTC Brain Cancer Module-20 (EORTC QLQ-BN20), and the St. Louis University Mental Status (SLUMS) examination.

Each patient was paired to a historical control who had received SRS without HBO, matched on the basis of histology, histology-specific graded prognostic assessment (GPA), resection status, and lesion size (>=2.0 cm vs < 2.0 cm). Two SRS + HBO patients with melanoma diagnoses could not be matched exactly by lesion size – both had lesions slightly below 2.0 cm but were matched to controls each at 2.5 cm. In two other cases the GPAs of the control patients were one step higher (better) than the GPAs of the corresponding SRS + HBO patients.

Data collection and statistical analysis

Local recurrence (LR), radionecrosis (RN), and intracranial distant recurrence (DR) were analyzed on the basis of standard pre- and post-contrast MRI, dynamic susceptibility contrast perfusion images, relative apparent diffusion coefficient, single voxel proton spectroscopy, and temporal evolution. A neuroradiologist, blinded to treatment type, analyzed all MRI images for LR, RN, and DR, and these were compared temporally across time for validation and consistency. LR was defined as new or enlarging abnormality with a pattern of elevated cerebral blood volume, ADC ratio < 1.7, or choline:creatine ratio > 2.0 on follow-up MRI imaging. RN was defined as any new nodular, enduring enhancement that was found not to be LR. DR was defined as any emerging evidence of metastatic disease within brain tissue not treated by SRS. The histology-specific GPA score was calculated for each patient using scales developed by the Radiation Therapy Oncology Group (RTOG) [13].

Statistical analyses were performed with SAS version 9.4 software (SAS Institute, Cary, NC) and with MATLAB version 2018b (The Mathworks Inc., Natick, MA). Overall survival (OS), time to LR, time to LR before WBRT, time to RN, time to RN before WBRT, and time to DR before WBRT were analyzed using the Kaplan-Meier method and were compared across both cohorts using the log-rank test; multivariate Cox proportional hazard modeling was used to analyze the effects of multiple parameters on these variables. For OS analysis, patients were scored as a failure at time of death or censored at last documented follow-up. For analyses of radiographic outcomes (time to RN, LR, or DR), patients were scored as a failure at time of RN, LR, or DR (respectively), or if failure did not occur, then they were censored at (1) time of death or (2) time of last follow-up, whichever occurred first. "Before WBRT" radiographic outcomes were analyzed as above, except that the patient also was censored and removed from analysis at time of WBRT, if WBRT occurred prior to the radiographic failure in question. Quality-of-life (QOL) data were analyzed using a linear mixed effect model with time after the pre-treatment assessment as the fixed effect and the repeated measures from individual subjects as random effects. With a focus on safety, only relatively large increases in risk of radionecrosis were included in the sample size calculation for the study, namely detection of a hazard ratio attributable to HBO of 2.6 or greater versus a matched cohort without HBO. Confidence intervals for hazard ratios in addition to p-values have been provided to further clarify interpretation of the results.

Results

Table 1 summarizes baseline patient, lesion, and treatment characteristics. From 2013 to 2018, of 22 patients enrolled, three were found ineligible, resulting in 19 treated with SRS + HBO. Of these 19, six patients underwent simultaneous SRS treatment for two lesions, yielding a total of 25 lesions treated with SRS + HBO. The matched historical control group who underwent SRS without HBO consisted of 19 patients with 27 metastatic lesions. In the control group, one patient had two lesions, two had three lesions, and one had four lesions that were treated simultaneously. Among all patients, only 3 lesions had PTVs greater than 4.0 cm diameter, all of which were based on postoperative cavities.

Median follow-up was 16.6 months (range 5.6 – 54.0 months) for the SRS + HBO group, while median follow-up was 12.4 months (range 2.0 – 43.3 months) for the SRS-only group.

The average time between leaving the HBO chamber and SRS beam-on was 8.3 (±1.7) minutes (range 5–12 minutes), with this interval shortening as operator experience increased: the first five patients' time interval averaged 10.2 (±1.2) minutes, whereas the average interval for the last five was 6.4 (±0.8) minutes.

RN was observed in 6 out of 25 lesions (24%) in the SRS + HBO group and 6 out of 27 lesions (22%) in the SRS-only group. The one-year Kaplan-Meier rates for freedom from RN before WBRT (RNBWFS) were 78% for SRS + HBO (95% CI: 0.45–0.93), versus 60% for SRS-only (95% CI: 0.29–0.81), and the median time to RNBWFS was 24.6 months versus 19.4 months respectively, but

Table 1
Baseline characteristics.

	n (%) or Mean (Min, Max)		
	SRS + HBO N = 19 patients	**SRS only** N = 19 patients	p-value
PATIENT-SPECIFIC DATA			
Age in years at SRS	62.2 (35, 78)	62.0 (23, 79)	0.86
Days from surgery to SRS	32.3 (21, 48)	36.8 (14, 90)	0.63
Female sex	9 (48%)	6 (32%)	0.06
Extracranial metastasis present	13 (68%)	14 (74%)	0.36
Breast Cancer Histology	2 (11%)	2 (11%)	1.00
Subsequent WBRT	5 (26%)	2 (11%)	0.40
KPS at time of SRS:			
100	1 (5%)	1 (5%)	
90	13 (68%)	13 (68%)	
80	4 (21%)	5 (26%)	
70	1 (5%)	0 (0%)	
# of Metastases at time of SRS:			
1	11 (58%)	15 (79%)	
2	7 (37%)	1 (5%)	
3	0 (0%)	3 (16%)	
4	1 (5%)	0 (0%)	
LESION-SPECIFIC DATA	**N = 25 lesions**	**N = 27 lesions**	
PTV (in milliliters)	7.6 (0.3, 25.7)	8.5 (0.2, 40.5)	0.72
Delivered Dose (in Gray)	17.6 (12.0, 20.0)	17.0 (12.0, 20.0)	0.47
Lesions resected	8 (32%)	9 (33%)	1.00
Breast Cancer Histology	3 (12%)	2 (7%)	0.66
Tumor Diameter in cm	1.8 (0.5, 4.5)	1.8 (0.2, 4.9)	0.80
Tumors over 2.0 cm	10 (40%)	14 (52%)	0.42
Tumor Diameters:			
0–0.9 cm	8 (32%)	9 (33%)	
1.0–1.9 cm	7 (28%)	4 (15%)	
2.0–2.9 cm	6 (24%)	13 (48%)	
3.0–3.9 cm	2 (8%)	0 (0%)	
4.0–5.0 cm	2 (8%)	1 (4%)	

the groups were not significantly different per Kaplan-Meier log-rank test (p = 0.60, Fig. 1). Results were similar for freedom from RN (regardless of WBRT) with 1-year estimated radionecrosis-free survival rates trending in favor of SRS + HBO, though not statistically significant: RNFS – 83% for SRS + HBO (95% CI: 0.55–0.94), versus 60% for SRS-only (95% CI: 0.29–0.81).

QOL measures were evaluated at each follow-up visit, with severities of solicited AEs scored using Common Terminology Criteria for Adverse Events (CTCAE v4.0). Grade I and II solicited AEs with an attribution of at least "possibly" treatment-related were observed in both cohorts – 16 in five patients treated with HBO and SRS and 17 in five patients treated with SRS only – but Grade III and IV treatment-related, solicited AEs were not found in either group (Supplementary Table 1 and Supplementary Fig. 1). Linear mixed model analyses of both the EORTC Global Health Status (QL2) and of the SLUMS metrics showed no statistically significant changes following SRS + HBO (Supplementary Figs. 2 and 3).

Local control was achieved in 23 out of 25 lesions (92%) in the SRS + HBO group and 23 out of 27 lesions (85%) in the SRS-only group (p = 0.67). The one-year Kaplan-Meier estimates of rates of patients LR-free before WBRT (LRBWFS) were 95% for SRS + HBO (95% CI: 0.68–0.99), and 78% for SRS-only (95% CI: 0.49–0.91), but the median time to LRBWFS was not reached for either group. The treatment groups were not significantly different by Kaplan-Meier log-rank test (p = 0.36, Fig. 2).

A total of 7 out of 38 patients (18%) underwent WBRT subsequent to SRS treatment: 5 in the HBO group, 2 in the controls (p = 0.40). In all but one WBRT patient, distant recurrence in the brain arose prior to WBRT. Intracranial distant recurrence (DR) developed in 9 patients (47%) following HBO + SRS treatment versus 11 patients (58%) following SRS-only). The one-year Kaplan-Meier rates for freedom from DR before WBRT (DRBWFS) were 61% (95% CI: 0.35–0.79) and 57% (95% CI: 0.29–0.77), respectively – not statistically different per Kaplan-Meier log-rank test (p = 0.86, Fig. 3).

Estimated overall survival (OS) rates at one-year were 73% (95% CI: 0.47–0.88) for the SRS + HBO group and 56% (95% CI: 0.31–0.75) for the SRS-only group. Median survival times were 17.0 months with HBO versus 12.4 months without HBO, but Kaplan-Meier log-rank analysis did not find a significant mortality difference between the treatment groups (p = 0.25, Fig. 4).

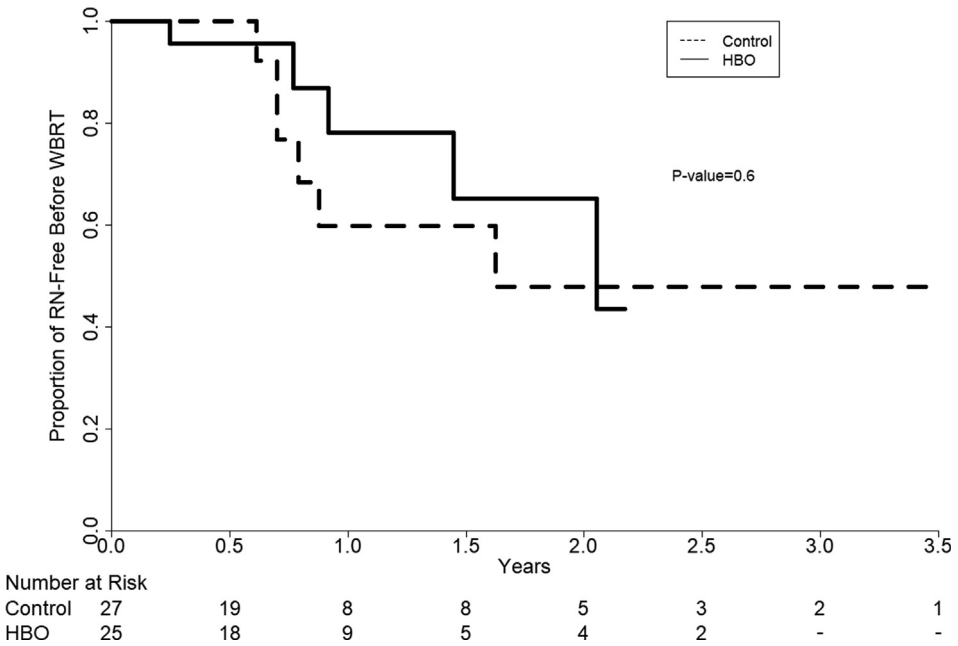

Fig. 1. Kaplan-Meier analysis of freedom from radionecrosis before WBRT (RNBWFS) stratified by lesions treated with HBO prior to SRS. *p*-value = 0.6 calculated from log-rank test.

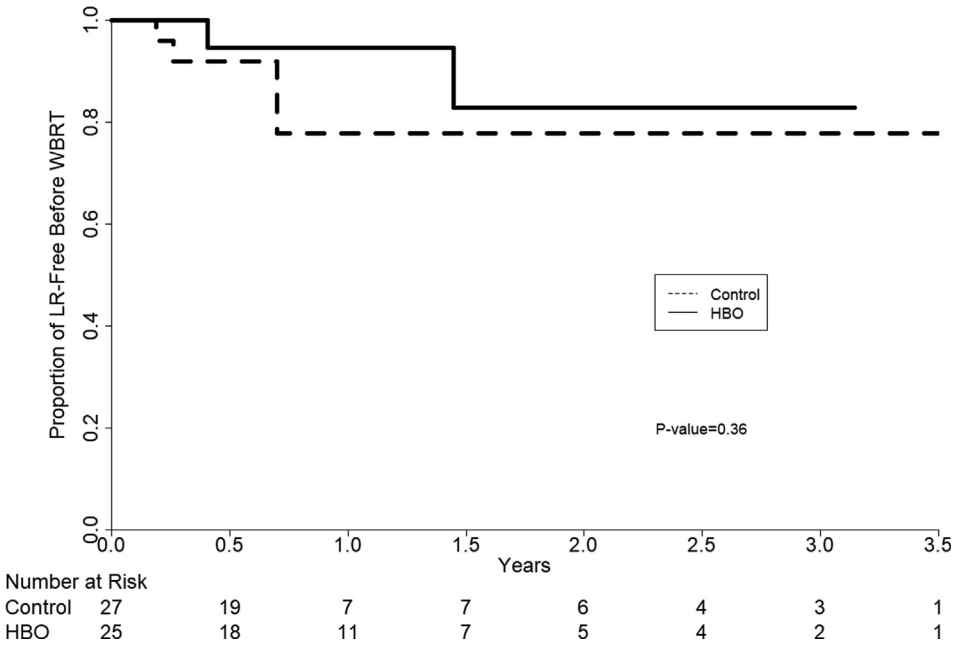

Fig. 2. Kaplan-Meier analysis of freedom from local recurrence before WBRT (LRBWFS) stratified by lesions treated with HBO prior to SRS. *p*-value = 0.36 calculated from log-rank test.

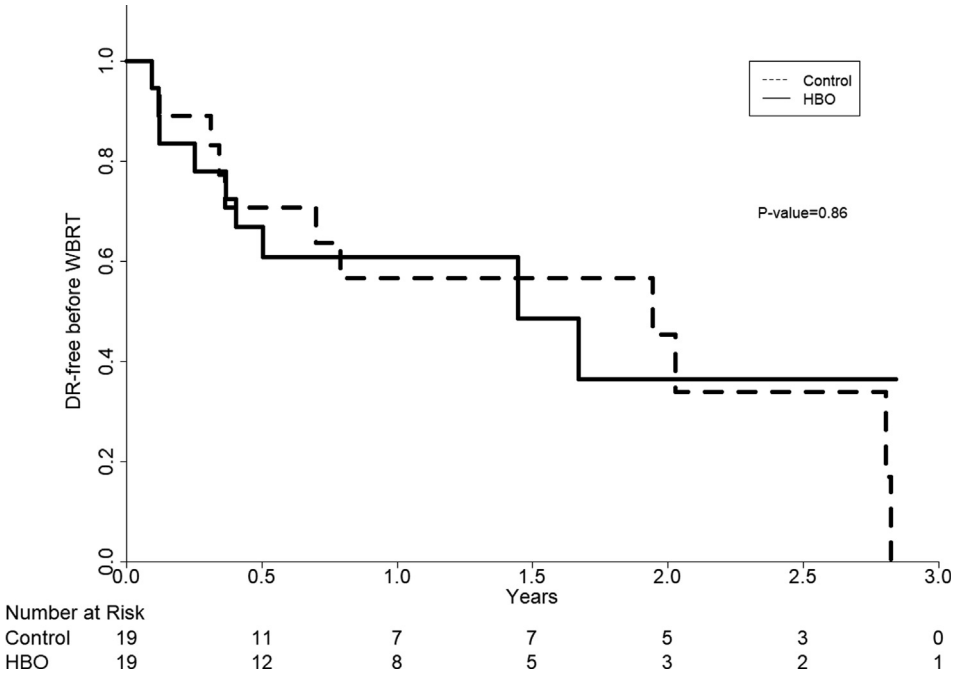

Fig. 3. Kaplan-Meier analysis of freedom from intracranial distant recurrence before WBRT (DRBWFS) stratified by lesions treated with HBO prior to SRS. *p*-value = 0.86 calculated from log-rank test.

Multivariate Cox regression models for LRBWBFS, RNBWFS, DRBWFS, and OS, did not show HBO to be a significant predictor of any of these clinical outcomes (Table 2), likely underpowered to do so. However, statistically significant relationships ($p \leq 0.05$) included: (1) higher PTV volume correlated with local recurrence (LRBWFS), (2) tumor resection correlated with radionecrosis (RNBWFS); (3) tumor resection correlated with overall survival (OS); and (4) higher GPA correlated with overall survival (OS).

Discussion

Over prior decades, concern has been raised that HBO combined with radiation therapy may contribute to radionecrosis of surrounding normal structures for a variety of sites. For example, a recent Cochrane review of seven trials (1978–1999) with 779 participants found a statistically significant increase in chance of severe radiation tissue injury following HBO with a relative-risk of

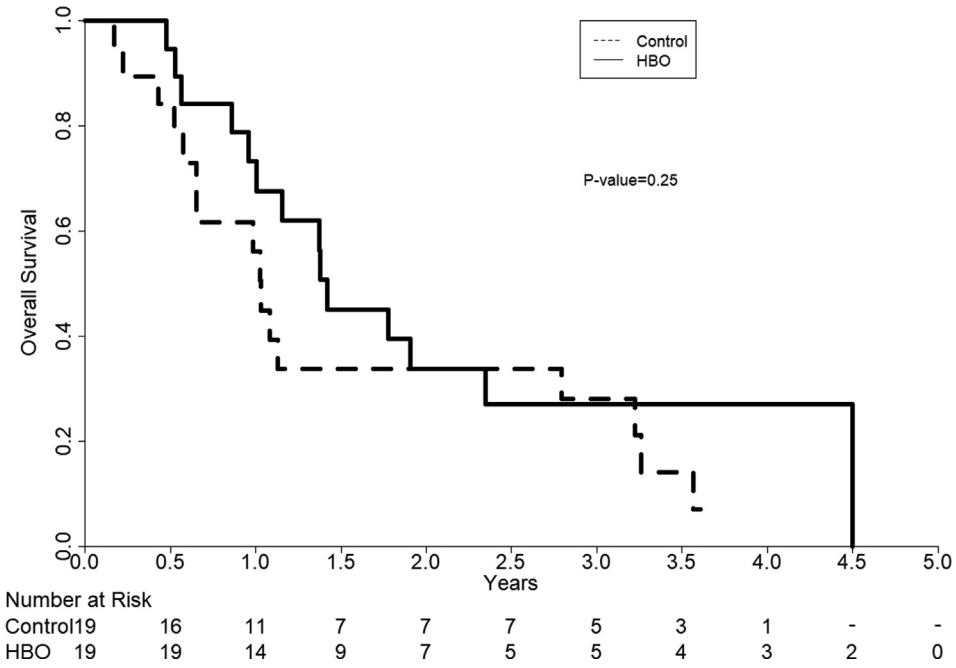

Fig. 4. Kaplan-Meier analysis of overall survival (OS) stratified by lesions treated with HBO prior to SRS. *p*-value = 0.25 calculated from log-rank test.

Table 2
Hazard Ratios (with p-values) for factors in multivariate Cox regression analyses.

Factor	HR [95% CI] for each factor in the given multivariate Cox regression (p-value)			
	LR prior to WBRT	RN prior to WBRT	DR prior to WBRT	Mortality (=1-OS)
HBO (dichotomous)	0.67 [0.11–4.19] (0.67)	0.82 [0.23–2.95] (0.76)	0.87 [0.35–2.15] (0.76)	0.57 [0.26 – 1.25] (0.16)
Resected (dichotomous)	0.06 [0.00–1.23] (0.07)	**5.12 [1.17–22.35] (0.03)**	0.48 [0.15–1.49] (0.20)	**0.33 [0.12–0.92] (0.03)**
PTV (in milliliters)	**1.10 [1.00–1.20) (0.05)**	0.98 [0.92–1.05] (0.59)	0.98 [0.92–1.05] (0.65)	-
Size Over 2-cm (dichotomous)	-	-	-	1.08 [0.42–2.79] (0.87)
Number of brain metastases	-	-	1.92 [0.96–3.83] (0.07)	-
GPA	-	-	-	**0.48 [0.29–0.80] (0.005)**
Breast cancer histology (dichotomous)	-	-	-	1.77 [0.55–5.72] (0.34)

Abbreviations: HR = hazard ratio; CI = confidence interval; LR = local recurrence; WBRT = whole brain radiation therapy; RN = radionecrosis; DR = distant recurrence; OS = overall survival; HBO = hyperbaric oxygen; PTV = planning target volume; GPA = graded prognostic assessment.
Notes: HBO, resection status, size over 2-cm, GPA, and histology other than breast cancer were treated as categorical variables, while PTV and number of brain metastases were treated as continuous variables. The model for OS included a separate variable for breast histology due to its relative survival advantage in the RTOG's GPA-breast subscale.[11] Boldfaced underlined values have *p*-value $\leq$ 0.05.

2.35 (CI 1.66 to 3.33) [9]. Nevertheless, no worsened toxicities were found in a recent multicenter Phase I trial of patients with Stage IVa oropharyngeal cancers treated with HBO plus aggressive full-course chemotherapy and radiation therapy – in the context of modern planning and delivery techniques [10].

Similarly, this current phase I clinical trial showed no increased risk of radionecrosis (nor other radiographic or clinical toxicity) with the addition of HBO to standard full-dose SRS for brain metastases – including both native and post-operative tumor targets, and including both tumors greater and less than 2-cm diameter – as compared to a control cohort matched for histology, size, GPA, and resection status. In addition, clinical outcomes such as LC, DR, or OS trended better with the addition of HBO compared with controls, although these differences were not significant.

SRS control of brain metastases worsens with increasing lesion size [12,14]. Tumor hypoxia may play a role in this relationship, as larger tumors tend to be more hypoxic, and opportunity for re-oxygenation is reduced with fewer fractions [15]. HBO may offer a potential solution, in that HBO may increase pO2 levels in brain lesions and in peritumoral brain tissue, with elevated levels maintained 15 minutes after HBO in both regions [16].

For more than six decades researchers have explored HBO and other methods for improving tumor pO2 levels to circumvent radioresistance [17–19]. Clinical trials have evaluated administra-

tion of HBO prior to fractionated radiation therapy in the treatment of malignant gliomas and of single brain metastases [20–23]. However, to our knowledge no study to date has explored the combination of HBO with SRS.

We hypothesize that the addition of HBO to SRS for large brain metastases may improve local control without worsening toxicities. A phase II trial is under development to study the addition of HBO to SRS in the preoperative setting, thereby enabling evaluation not just of clinical outcomes, but of the underlying cellular pathophysiology of the lesions irradiated with and without HBO.

Conclusion

Delivery of HBO immediately prior to intracranial SRS is feasible. It proved safe without incidents of grade III or IV toxicities and without worsened radionecrosis, tumor control, survival, or QOL. This study supports further investigation into using HBO as a radiosensitizer to supplement SRS treatment.

Clinical trial information

The ClinicalTrials.gov identifier for this study is NCT01850563.

The trial and its supporting documents were reviewed, approved, and supervised by the Dartmouth-Hitchcock Institutional Review Board, (603) 650-1846.

Data sharing statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Results of this study were presented in part as a poster (#11) at the 100th Annual Meeting of the American Radium Society, May 5–8, 2018, Orlando, FL, and also as a poster (#2172) at the 61st Annual Meeting of the American Society for Radiation Oncology, September 15–18, 2019, Chicago, IL.

Conflict of Interest

None declared.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.10.024.

References

[1] Sacks P, Rahman M. Epidemiology of brain metastases. Neurosurg Clin N Am 2020;31:481–8.
[2] Graber JJ, Cobbs CS, Olson JJ. Congress of Neurological Sureons systematic review and evidence-based guidelines on the use of stereotactic radiosurgery in the treatment of adults with metastatic brain tumors. Neurosurgery 2019;84:E168–70.
[3] Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation:a randomised controlled trial. Lancet Oncol 2009;10:1037–44.
[4] Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol 2017;18:1049–60.
[5] Nieder C, Grosu AL, Gaspar LE. Stereotactic radiosurgery (SRS) for brain metastases: a systematic review. Radiat Oncol 2014;9:155–63.
[6] Brown JM, Diehn M, Loo BW. Stereotactic ablative radiotherapy should be combined with a hypoxic cell radiosensitizer. Int J Radiat Oncol Biol Phys 2010;78:323–7.
[7] Carlson DJ, Keall PJ, Loo BW, Chen ZJ, Brown JM. Hypofractionation results in reduced tumor cell kill compared to conventional fractionation for tumors with regions of hypoxia. Int J Radiat Oncol Biol Phys 2011;79:1188–95.
[8] Hall EJ, Giaccia AJ. Oxygen Effect and Reoxygenation. In: Radiobiology for the Radiologist. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012. p. 86–103.
[9] Bennett MH, Feldmeier J, Smee R, Milross C. Hyperbaric oxygenation for tumour sensitisation to radiotherapy. Cochrane Database Syst Rev 2018;4:CD005007.
[10] Hartford AC, Davis TH, Buckey JC, et al. Hyperbaric oxygen as radiation sensitizer for locally advanced squamous cell carcinoma of the oropharynx: A phase 1 dose-escalation study. Int J Radiat Oncol Biol Phys 2017;97:481–6.
[11] Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90–05. Int J Radiat Oncol Biol Phys 2000;47:291–8.
[12] Hartford AC, Paravati AJ, Spire WJ, et al. Postoperative stereotactic radiosurgery without whole-brain radiation therapy for brain metastases: potential role of preoperative tumor size. Int J Radiation Oncol Biol Phys 2013;854:650–5.
[13] Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol 2012;30:419–25.
[14] Moraes FY, Winter J, Eshetu G, et al. Outcomes following stereotactic radiosurgery for small to medium-sized brain metastases are exceptionally dependent upon tumor size and prescribed dose. NeuroOnc 2019;21:242–51.
[15] Li S, Shen L. Radiobiology of stereotactic ablative radiotherapy (SABR): perspectives of clinical oncologists. J of Cancer 2020;11:5056–8.
[16] Beppu T, Kamada K, Yoshida Y, et al. Change of oxygen pressure in glioblastoma tissue under various conditions. J Neuroonc 2002;548:47–52.
[17] Gray LH, Conger AD, Ebert M, Hornsey S, Scott OC. The concentration of oxyhgen dissolved in tissues at the time of irradiation as a factor in radiotherapy. Br J Radiol 1953;26:638–48.
[18] Overgaard J, Horsman MR. Modification of hypoxia-induced radioresistance in tumors by trhe use of oxygen and sensitizers. Semin Radiat Oncol 1996;6:10–21.
[19] Overgaard J. Hypoxi radiosensitization: adored and ignored. J Clin Oncol 2007;25:4066–74.
[20] Beppu T, Kamada K, Nakamura R, et al. A phase II study of radiotherapy after hyperbaric oxygenation combined with interferon-beta and nimustine hydrochloride to treat supratentorial malignant gliomas. J Neurooncol 2003;61:161–70.
[21] Kohshi K, Yamamoto H, Nakahara A, Katoh T, Takagi M. Fractionated stereotactic radiotherapy using gamma unit after hyperbaric oxygenation on recurrent high-grade gliomas. J Neurooncol 2007;82:297–303.
[22] Ogawa K, Ishiuchi S, Inoue O, et al. Phase II Trial of radiotherapy after hyperbaric oxygenation with multiagent chemotherapy (procarbazine, nimustine, and vincristine) for high-grade Gliomas: long-term results. Int J Radiat Oncol 2012;82:732–8.
[23] Tao J, Gao Z, Huang R, Li H. Therapeutic effect of combined hyperbaric oxygen and radiation therapy for single brain metastasis and its influence on osteopontin and MMP-9. Exp Ther Med 2019;17:465–71.