Cancer & Hyperbaric Oxygen Therapy

Hyperbaric Oxygen Combined With Ketogenic Diet Enhances The Fight

- Our focus is to 'assist and support' those with this complex illness - we encourage all individuals and family members to undertake due diligence and keep an open mind on the subject.

- Hyperbaric Oxygen (HBO) is NOT provided to 'treat the cancer or diminish the spread of cancer mutation'.

- HBO is provided to assist the patient whilst undertaking conservative orthodox and complimentary approaches.

- Key factors driving cancer resistance include Hypoxia (low oxygen tension is the hallmark of solid tumors) associated with elevated inflammatory 'biomarkers' Cytokines (IL1, 6, 7, 8) including Tumour Necrosis Factor alpha (TNFα), GlycA, chronic anaerobic and fungal infections, high carbohydrate, high glucose diet ...

- Lifestyle Factors include: Ketogenic Diet, MCT Oil (Medium Chain Triglyceride Oil), Metformin (inhibits Interleukin 8 & TNFa), Mistletoe, Curcumin (blocks cytokine inflammation), Sodium Bicarbonate - Alkalinity, N-Acetyl Cysteine (NAC) (inhibits cytokine inflammation), Low Dose Naltrexone.

- Hyperbaric Oxygen impacts cellular Oxygen tension and inflammatory cascades and has been shown to 'enhance the efficacy of radiotherapy and chemotherapy for the treatment of malignant tumors'. Undersea Hyperb Med. (2013).

- Hyperbaric Oxygen Therapy does not promote metastasis – It Is the opposite - Hypoxia increases tumorgenesis & resistance to conventional treatments - Hyperbaric Oxygen Therapy and Cancer Growth (UHMS 2003).

- 'Hyperbaric Oxygen Therapy is the 'integrative bridge' between orthodox and complementary approaches. The human frame is Oxygen dependent. Oxygen is essential to quality of life and essential to drug delivery. This multifactor internal healing response is 'unique'.

Common Cancer Markers

Some of our most popular tumor marker antibodies include:

- CA 50 antibody: CA-50 is a widely used tumor marker mainly found in gastro-intestinal carcinomas. Testing for CA50 is more useful for determining the effectiveness of treatment, rather than for cancer screening. This CA 50 antibody is a purified IgM and is specific for the human cancer antigen 50.
- CA 125 antibody: Another of our most popular cancer antigen antibodies, CA 125 (MUC16) is the most frequently used biomarker for ovarian cancer detection. This CA 125 antibody is suitable for use both in ELISA and immunohistochemistry.
- CA 19-9 antibody: CA 19-9 is commonly found in elevated levels in the blood of patients suffering from colon and pancreatic cancer. This CA 19-9 antibody can be used in both ELISA and Immunohistochemistry.

- PSA antibody: PSA or Prostate Specific Antigen was one of the earliest discovered cancer biomarkers. The blood level of PSA is often elevated in men with prostate cancer. When used in screening, the PSA test can help detect small tumors that do not cause symptoms.

Hyperbaric Oxygen Therapy & Ketogenic Diet

The Ketogenic Diet and Hyperbaric Oxygen Therapy prolonged survival (by 78%) with Systemic Metastatic Cancer
"Mice exposed to combined ketogenic diet and hyperbaric oxygen therapy lived 78 percent longer than mice fed a standard high-carbohydrate diet." Source: Research team from the Hyperbaric Biomedical Research Laboratory at the University of South Florida.
"When administered properly, both the ketogenic diet and hyperbaric oxygen therapy are non-toxic and may even protect healthy tissues while simultaneously damaging cancer cells," said Prof D'Agostino.

HYPERBARIC OXYGEN, KETOGENIC DIET & CANCER SURVIVAL

Historical Understanding of Cancer Metabolism
Dr. Otto Warburg Nobel Prize winner

Cancer cells are known to be anaerobic, meaning they ferment oxygen rather than burn oxygen. When the level of oxygen that gets into a normal cell becomes too low, or the ATP molecule count gets too low, a normal cell will convert into becoming anaerobic. A Nobel Prize was awarded for proving that cancer cells are anaerobic, meaning they do not burn glucose, but rather they ferment glucose in order to get their ATP energy.

- “Over seventy-five years ago Dr. Otto Warburg published a Nobel Prize winning paper describing the environment of the cancer cell. A normal cell undergoes an adverse change when it can no longer take up oxygen to convert glucose into energy by oxidation. In the absence of oxygen the cell reverts to a primitive nutritional program to sustain itself, converting glucose, by fermentation. The lactic acid produced by fermentation lowers the cell pH (acid/alkaline balance) and destroys the ability of DNA and RNA to control cell division - the cancer cells begin to multiply unchecked. The lactic acid simultaneously causes intense local pain and destroys cell enzymes. Therefore, cancer appears as a rapidly growing outer cell mass with a core of dead cells.”

- In the absence of oxygen, glucose undergoes fermentation to create lactic acid. This causes the cell pH to drop from between 7.3 to 7.2 down to 7 and later to 6.5; in more advanced stages of cancer and in metastases the pH may drop to 6.0 and even 5.7.

- Dr. Warburg stated: “But nobody today can say that one does not know what cancer and its prime cause be. On the contrary, there is no disease whose prime cause is better known, so that today ignorance is no longer an excuse that one cannot do more about prevention. That prevention of cancer will come there is no doubt, for man wishes to survive. But how long prevention will be avoided depends on how long the prophets of agnosticism will succeed in inhibiting the application of scientific knowledge in the cancer field. In the meantime, millions of men must die of cancer unnecessarily." [Nobel Prize

Winner Otto Warburg in a meeting of Nobel Laureates, June 30, 1966]. http://www.cancertutor.com/

Alkalinity

Acidity generated by the tumor microenvironment drives local invasion
Estrella V, Chen T, Lloyd M, Wojtkowiak J, Cornnell HH, Ibrahim-Hashim A, Bailey K, Balagurunathan Y, Rothberg JM, Sloane BF, Johnson J, Gatenby RA, Gillies RJ.
Source
Departments of Cancer Imaging and Metabolism, Radiology, and Analytic Microscopy Laboratory, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA.
Abstract
The pH of solid tumors is acidic due to increased fermentative metabolism and poor perfusion.
It has been hypothesized that acid pH promotes local invasive growth and metastasis. The hypothesis that acid mediates invasion proposes that H(+) diffuses from the proximal tumor microenvironment into adjacent normal tissues where it causes tissue remodeling that permits local invasion.
In the current work, tumor invasion and peritumoral pH were monitored over time using intravital microscopy. In every case, the peritumoral pH was acidic and heterogeneous and the regions of highest tumor invasion corresponded to areas of lowest pH.
Tumor invasion did not occur into regions with normal or near-normal extracellular pH. Immunohistochemical analyses revealed that cells in the invasive edges expressed the glucose transporter-1 and the sodium-hydrogen exchanger-1, both of which were associated with peritumoral acidosis.
In support of the functional importance of our findings, oral administration of sodium bicarbonate was sufficient to increase peritumoral pH and inhibit tumor growth and local invasion in a preclinical model, supporting the acid-mediated invasion hypothesis. Cancer Res; 73(5); 1524-35. ©2012

Hypoxia Key Factor To Tumour Resistance and Tumour Proliferation

Hyperbaric Oxygenation of Hypoxic Glioblastoma Multiforme Cells Potentiates the Killing Effect of an Interleukin-13-Based Cytotoxin
IL13 has anti-tumour effects and when combined with HBO enhances the killing effects of Glioblastoma and other cancers.

Glioblastoma Multiforme is a high-grade astrocytoma and represents the most aggressive form of brain tumors. The successful treatment of patients with glioblastoma multiforme is still a major challenge, and a median survival rate is 14.5 months since diagnosis (1).

- 'Similarly to other solid tumors, glioblastoma multiforme tumors exhibit resistance to radiotherapy and chemotherapy largely in part due to the hypoxic tumor microenvironment'
- In addition to the aggressive invasive nature of glioblastoma multiforme is the unique property of tumor hypoxia (inadequate oxygen). Hypoxia is considered as an important factor affecting the efficacy of current orthodox treatments in glioblastoma multiforme (2, 3).
- Hypoxia is an alteration of balance between cellular proliferation and oxygen supply, resulting in significantly lower oxygen levels in focal regions than those encountered in surrounding both malignant and normal tissues (4).

- 'Hypoxia influences the behaviour of human tumor cells and empowers hypoxic tumour cells a higher resistance to radiotherapy and certain chemotherapies and a higher mutation rate and potential for a more metastatic and malignant phenotype'
- Evidence suggests that hypoxia influences the behavior of human tumor cells and empowers hypoxic tumor cells a higher resistance to radiotherapy and certain chemotherapies and a higher mutation rate and potential for a more metastatic and malignant phenotype (2).
- The tumor oxygenation is negatively associated with increasing grade of human astrocytomas (5).
- Similarly to other solid tumors, glioblastoma multiforme tumors exhibit strong resistance to radiotherapy and chemotherapy due to the hypoxic tumor microenvironment (6).

- Hyperbaric Oxygen Therapy (HBO) impacts cellular Oxygen tension and inflammatory cascades and has been shown to 'enhance the efficacy of radiotherapy and chemotherapy for the treatment of malignant tumors'. Undersea Hyperb Med. 2013.

Hyperbaric Oxygen Re-Oxygenation Effects

Several clinical trials have been done with Hyperbaric Oxygen or hypoxic cell radiosensitizers intending to overcome the problem of the radioresistance of hypoxic tumor cells (7–9). The results of these trials have shown benefit of proper oxygenation for glioblastoma multiforme radiotherapy. 'Our results show that a recombinant cytotoxin directed against glioblastoma multiforme cells kills these cells much less efficiently under anoxic/hypoxic conditions.

- The HBO reoxygenation brings unexpected additional rebound benefit (IL13) making glioblastoma multiforme cells even more responsive to the killing effect of a cytotoxin.'

- The reoxygenated anoxic glioblastoma multiforme cells were 2- to 10-fold more sensitive to DT-IL13QM killing than normoxic glioblastoma multiforme cells.
- IL-13 expression in glioblastoma multiforme cells is dependent on oxygenation status. IL-13 is up-regulated with HBO.
- Reoxygenation causes a 'rebound' or even a further increase in protein levels of IL-13Ra2 and active furin in glioblastoma multiforme cells subjected to anoxia or hypoxia.

Hypoxia & Glucose Fermentation Drives Tumour Growth

Thomas Seyfried: Cancer A Metabolic Disease With Metabolic Solutions

Does Hyperbaric Oxygen Therapy Cause Cancer Spread? No The Opposite ...

Hyperbaric Oxygen does it promote growth or recurrence of malignancy (UHMS 2003)?

Austin Hospital Melbourne - Hyperbaric Oxygen Therapy & Cancer Resistance

Hyperbaric oxygen therapy for malignancy 2006, by Daruwalla J, Christophi C. University of Melbourne, Austin Hospital, Level 8 Lance Townsend Building, Austin Health, Studley Road,

Heidelberg, Victoria, 3084 Australia received international recognition and formed the basis of numerous peer reviewed studies.

- Unfortunately, the Austin Hospital does NOT provide Hyperbaric Oxygen Therapy to assist cancer patients.
- Why isn't the Australian Government providing HBO funding to assist patient outcomes based on this internationally acclaimed study?
- HBO continues to be dictated by economic and political influences under the careful watch of pharmaceutical preferences.

Hyperbaric oxygen therapy for malignancy
World J Surg. 2006 Dec;30(12):2112-31.
Daruwalla J, Christophi C.
Source
Department of Surgery, University of Melbourne, Austin Hospital, Level 8 Lance Townsend Building, Austin Health, Studley Road, Heidelberg, Victoria, 3084 Australia. jurstine@pgrad.unimelb.edu.au
Abstract
One unique feature of tumors is the presence of hypoxic regions, which occur predominantly at the tumor center.
Hypoxia has a major impact on various aspects of tumor cell function and proliferation. Hypoxic tumor cells are relatively insensitive to conventional therapy (chemotherapy and radiation) owing to cellular adaptations effected by the hypoxic microenvironment. Recent efforts have aimed to alter the hypoxic state and to reverse these adaptations to improve treatment outcome.
One way to increase tumor oxygen tensions is by hyperbaric oxygen (HBO) therapy. HBO therapy can influence the tumor microenvironment at several levels. It can alter tumor hypoxia, a potent stimulus that drives angiogenesis. Hyperoxia as a result of HBO also produces reactive oxygen species, which can damage tumors by inducing excessive oxidative stress. This review outlines the importance of oxygen to tumors and the mechanisms by which tumors survive under hypoxic conditions. It also presents data from both experimental and clinical studies for the effect of HBO on malignancy.

HBO & Breast Cancer

Hyperbaric Oxygenation Potential Anti-Cancer Effects on Breast Cancer Cells
In the 2007 study, Haroon, Patel, and Al-Mehdi decided to evaluate the growth of murine breast cancer cells in the lung after hyperbaric oxygen treatment in an experimental metastasis assay. The total metastatic load in the lung is reduced after HBO - that’s one of the most significant new findings from a 2007 study ...

HBO & Aggressive Brain Tumours (Glioblastoma Multiforme)

Radiotherapy after hyperbaric oxygenation in malignant gliomas
Curr Med Res Opin. 2015 Sep 28:1-8. [Epub ahead of print]
Chen JR1, Xu HZ1, Ding JB1, Qin ZY1.

Author information

Abstract
This review was to evaluate the efficacy and toxicity of radiation therapy (RT) administered immediately after hyperbaric oxygen (HBO) therapy in patients with high grade gliomas.
RESEARCH DESIGN AND METHODS:
PubMed, Embase, ISI Web of Knowledge, and Cochrane databases were searched using combinations of the following search terms: radiotherapy, hyperbaric oxygenation, chemotherapy, glioma, brain tumor. Selection was limited to prospective studies involving patients given HBO followed by RT for high-grade gliomas. Data extracted from studies included the clinical research phase of the study, number of study arms, number of patients, patient age and gender, glioma type and grade, pressure and length of HBO, protocol of radiation therapy, duration of follow-up, and the outcomes.
MAIN OUTCOME MEASURES:
Overall survival, time to progression, response rate, tumor regression, and toxic effects associated with HBO plus RT treatment.
RESULTS:
Literature search/screening yielded eight studies for analysis. Six of the studies were single-arm in design and enrolled a total of 203 patients, of whom 142 had grade IV gliomas and 61 had grade III gliomas. In these six studies, all patients received HBO then RT. Two studies were double-arm in design, with 24 patients treated with HBO followed by RT and 26 patients treated with RT alone.
The findings from both the single- and double-arm studies indicated improved outcomes (survival rate, progression free survival, time to progression, response rate) with HBO and RT therapy. Reported toxicity included leucopenia, anemia, thrombocytopenia, fever, loss of appetite, constipation, nausea, vomiting, and liver dysfunction. The addition of HBO had minimal effect on toxicity or side effects; across the eight studies, only one patient with severe middle ear barotrauma had a complication directly related to HBO exposure.
CONCLUSION:
This systematic reviews suggests that the addition of HBO to RT is tolerated and may be beneficial in patients with high-grade gliomas.

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HBO & Mild Hyperthermia

Int J Hyperthermia. 2015 Jul 9:1-6. [Epub ahead of print]
Efficacy of hyperbaric oxygen therapy combined with mild hyperthermia for improving the anti-tumour effects of carboplatin
Ohguri T1, Kunugita N, Yahara K, Imada H, Uemura H, Shinya N, Youjirou G, Takashi C, Okazaki R, Ootsuyama A, Korogi Y.
Author information

Abstract
PURPOSE:
The aim of this study was to evaluate the effects of hyperbaric oxygen therapy (HBO) on the enhancement of hyperthermic chemosensitisation to carboplatin at mild temperatures in experimental tumours.
METHODS:
SCCVII carcinoma in C3H/He mice was used to assess tumour growth delay. The mice received intraperitoneal injections of carboplatin.
For HBO treatment, the mice were exposed to HBO at 2.0 atmospheres of absolute oxygen for 60 min. For mild hyperthermia (HT), treatment at 41.5 °C for 30 min was performed. The

tumour tissue pO2 levels were measured with a digital pO2 monitor during and immediately after treatment.
RESULTS:
The average time taken to reach a threefold relative tumour size was significantly longer after treatment with carboplatin combined with mild HT and HBO than after treatment with carboplatin and mild HT. The relative sizes of the tumours after the combined treatment were smallest when the treatment sequence was carboplatin, mild HT, and HBO.
The tumour tissue pO2 values were significantly higher immediately after mild HT followed by HBO than immediately after HBO followed by mild HT. The tumour tissue pO2 levels during mild HT and HBO generally increased, although the patterns of the increases varied.
CONCLUSION:
The administration of HBO increased the effects of hyperthermic chemosensitisation to carboplatin at mild temperatures on experimental tumours, particularly when given in the sequence of carboplatin, mild HT, and HBO, a finding that supports previous clinical outcomes for a novel combined therapy using carboplatin plus HT and HBO.
1Department of Radiology, University of Occupational and Environmental Health , Kitakyushu , Japan .

HBO & Vitamin C

Wien Med Wochenschr. 2015 Jun;165(11-12):251-257. Epub 2015 Jun 12.
Molecular mechanisms of pharmacological doses of ascorbate on cancer cells
Venturelli S1, Sinnberg TW, Niessner H, Busch C.
Author information
Abstract
Intravenous application of high-dose ascorbate (vitamin C) has been used in complementary medicine since the 1970s to treat cancer patients. In recent years it became evident that high-dose ascorbate in the millimolar range bears selective cytotoxic effects on cancer cells in vitro and in vivo. This anticancer effect is dose dependent, catalyzed by serum components and mediated by reactive oxygen species and ascorbyl radicals, making ascorbate a pro-oxidative pro-drug that catalyzes hydrogen peroxide production in tissues instead of acting as a radical scavenger.

- It further depends on HIF-1 signaling and oxygen pressure, and shows a strong epigenetic signature (alteration of DNA-methylation and induction of tumor-suppressing microRNAs in cancer cells).

The detailed understanding of ascorbate-induced antiproliferative molecular mechanisms warrants in-depth preclinical evaluation in cancer-bearing animal models for the optimization of an efficacious therapy regimen (e.g., combination with hyperbaric oxygen or O2-sensitizers) that subsequently need to be evaluated in clinical trials.
1Department of Internal Medicine I, Medical University Hospital, Tuebingen, Germany.

Latest Clinical Reseach

Diving Hyperb Med. 2016 Jun;46(2):124.
Pre-emptive treatment with hyperbaric oxygen following radiation therapy for head and neck cancer may prevent the onset of late radiation tissue injury.
Wood D, Bennett M.
Comment on

- Early hyperbaric oxygen therapy for reducing radiotherapy side effects: early results of a randomized trial in oropharyngeal and nasopharyngeal cancer. [Int J Radiat Oncol Biol Phys. 2009]

J Am Chem Soc. 2016 Apr 27;138(16):5222-5. doi: 10.1021/jacs.6b01784. Epub 2016 Apr 13.
An Implantable Depot That Can Generate Oxygen in Situ for Overcoming Hypoxia-Induced Resistance to Anticancer Drugs in Chemotherapy.
Huang CC, Chia WT1, Chung MF, Lin KJ, Hsiao CW, Jin C, Lim WH, Chen CC, Sung HW.
Author information

- 1Department of Orthopaedics, National Taiwan University Hospital, Hsinchu Branch , Hsinchu 30013, Taiwan, ROC.

Abstract
In the absence of adequate oxygen, cancer cells that are grown in hypoxic solid tumors resist treatment using antitumor drugs (such as doxorubicin, DOX), owing to their attenuated intracellular production of reactive oxygen species (ROS). Hyperbaric oxygen (HBO) therapy favorably improves oxygen transport to the hypoxic tumor tissues, thereby increasing the sensitivity of tumor cells to DOX. However, the use of HBO with DOX potentiates the ROS-mediated cytotoxicity of the drug toward normal tissues. In this work, we hypothesize that regional oxygen treatment by an implanted oxygen-generating depot may enhance the cytotoxicity of DOX against malignant tissues in a highly site-specific manner, without raising systemic oxygen levels. Upon implantation close to the tumor, the oxygen-generating depot reacts with the interstitial medium to produce oxygen in situ, effectively shrinking the hypoxic regions in the tumor tissues. Increasing the local availability of oxygen causes the cytotoxicity of DOX that is accumulated in the tumors to be significantly enhanced by the elevated production of ROS, ultimately allaying the hypoxia-induced DOX resistance in solid malignancies. Importantly, this enhancement of cytotoxicity is limited to the site of the tumors, and this feature of the system that is proposed herein is unique.

Urology. 2016 Apr 25. pii: S0090-4295(16)30110-8. doi: 10.1016/j.urology.2016.04.015. [Epub ahead of print]
Evaluation of Hyperbaric Oxygen Therapy in the Treatment of Radiation-induced Hemorrhagic Cystitis.
Mougin J1, Souday V2, Martin F1, Azzouzi AR1, Bigot P3.
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Abstract
OBJECTIVE:
To evaluate the efficacy of hyperbaric oxygen therapy (HBO) in the treatment of postradiation hematuria (PRH) and to identify the predictive factors for a successful outcome.
MATERIALS AND METHODS:
We conducted a retrospective study and included all patients with PRH treated with HBO in a university hospital center between January 2003 and December 2013. We studied the patients' clinical characteristics, radiotherapy indication, treatments preceding HBO, the grade of hematuria diagnosed based on the Common Terminology Criteria for Adverse Events classification v 4.03 and the efficacy of HBO. The success of HBO was defined as the total or partial resolution of hematuria.

RESULTS:
We included 71 patients with a median age of 72 (39-87) years. PRHs were severe (grade ≥3) in 50 (70.4%) of the cases. Radiotherapy was indicated in the treatment of prostate cancer in 61 (85.9%) patients. The median length of time between hematuria and HBO was 8 (1-154) months. Prior to HBO, 46 (64.8%) patients underwent electrocoagulation of the bladder. HBO sessions were compounded by 9 cases of barotraumatic otitis, 5 cases of transient visual disturbance, and 1 case of finger paresthesia. On average, 29 (3-50) sessions were carried out. Treatment was effective in 46 (64.8%) patients, 37 (52.1%) of whom were completely cured. A hematuria grade of less than 3 was a predictive factor in the successful treatment (P = .027). Median follow-up was 15 (1-132) months.
CONCLUSION:
HBO completely resolves PRH in 52.1% of cases. Prolonged patient follow-up is required to confirm the efficacy of this treatment.

Cochrane Database Syst Rev. 2016 Apr 28;4:CD005005. doi: 10.1002/14651858.CD005005.pub4.
Hyperbaric oxygen therapy for late radiation tissue injury.
Bennett MH1, Feldmeier J, Hampson NB, Smee R, Milross C.
Author information
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Abstract
BACKGROUND:
Cancer is a significant global health problem. Radiotherapy is a treatment for many cancers and about 50% of people having radiotherapy will be long-term survivors. Some will experience late radiation tissue injury (LRTI) developing months or years later. Hyperbaric oxygen therapy (HBOT) has been suggested as a treatment for LRTI based upon the ability to improve the blood supply to these tissues. It is postulated that HBOT may result in both healing of tissues and the prevention of problems following surgery.
OBJECTIVES:
To assess the benefits and harms of HBOT for treating or preventing LRTI.
SEARCH METHODS:
We updated the searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 11), MEDLINE, EMBASE, DORCTIHM and reference lists of articles in December 2015. We also searched for ongoing trials at clinicaltrials.gov.
SELECTION CRITERIA:
Randomised controlled trials (RCTs) comparing the effect of HBOT versus no HBOT on LRTI prevention or healing.
DATA COLLECTION AND ANALYSIS:
Three review authors independently evaluated the quality of the relevant trials using the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and extracted the data from the included trials.
MAIN RESULTS:
Fourteen trials contributed to this review (753 participants). There was some moderate quality evidence that HBOT was more likely to achieve mucosal coverage with osteoradionecrosis (ORN) (risk ratio (RR) 1.3; 95% confidence interval (CI) 1.1 to 1.6, P value = 0.003, number needed to treat for an additional beneficial outcome (NNTB) 5; 246 participants, 3 studies). There was also moderate quality evidence of a significantly improved chance of wound breakdown without HBOT following operative treatment for ORN (RR 4.2; 95% CI 1.1 to 16.8, P value = 0.04, NNTB 4; 264 participants, 2 studies). From single studies there was a significantly increased chance of improvement or cure following HBOT for radiation proctitis (RR 1.72; 95% CI 1.0 to 2.9, P value = 0.04, NNTB 5), and following both

surgical flaps (RR 8.7; 95% CI 2.7 to 27.5, P value = 0.0002, NNTB 4) and hemimandibulectomy (RR 1.4; 95% CI 1.1 to 1.8, P value = 0.001, NNTB 5). There was also a significantly improved probability of healing irradiated tooth sockets following dental extraction (RR 1.4; 95% CI 1.1 to 1.7, P value = 0.009, NNTB 4).There was no evidence of benefit in clinical outcomes with established radiation injury to neural tissue, and no randomised data reported on the use of HBOT to treat other manifestations of LRTI. These trials did not report adverse events.
AUTHORS' CONCLUSIONS:
These small trials suggest that for people with LRTI affecting tissues of the head, neck, anus and rectum, HBOT is associated with improved outcome. HBOT also appears to reduce the chance of ORN following tooth extraction in an irradiated field. There was no such evidence of any important clinical effect on neurological tissues. The application of HBOT to selected participants and tissues may be justified. Further research is required to establish the optimum participant selection and timing of any therapy. An economic evaluation should be undertaken.

Lancet Oncol. 2016 Feb;17(2):224-33. doi: 10.1016/S1470-2045(15)00461-1. Epub 2015 Dec 17.
Hyperbaric oxygen for patients with chronic bowel dysfunction after pelvic radiotherapy (HOT2): a randomised, double-blind, sham-controlled phase 3 trial.
Glover M1, Smerdon GR2, Andreyev HJ3, Benton BE3, Bothma P4, Firth O5, Gothard L6, Harrison J7, Ignatescu M2, Laden G8, Martin S6, Maynard L9, McCann D10, Penny CE2, Phillips S10, Sharp G6, Yarnold J11.
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- 11Division of Radiotherapy and Imaging, Institute of Cancer Research, London, UK. Electronic address: John.yarnold@icr.ac.uk.

Abstract
BACKGROUND:
Hyperbaric oxygen has been used as a therapy for patients experiencing chronic intestinal syndromes after pelvic radiotherapy for decades, yet the evidence to support the use of this therapy is based almost exclusively on non-randomised studies. We aimed to provide conclusive results for the clinical benefits of hyperbaric oxygen in patients with chronic bowel dysfunction after radiotherapy for pelvic malignancies.
METHODS:
HOT2 was a double-blind, sham-controlled, phase 3 randomised study of patients (≥18 years) with chronic gastrointestinal symptoms for 12 months or more after radiotherapy and which persisted despite at least 3 months of optimal medical therapy and no evidence of cancer recurrence. Participants were stratified by participating hyperbaric centre and randomly assigned (2:1) by a computer-generated list (block size nine or 12) to receive treatment with hyperbaric oxygen therapy or sham. Participants in the active treatment group

breathed 100% oxygen at 2·4 atmospheres of absolute pressure (ATA) and the control group breathed 21% oxygen at 1·3 ATA; both treatment groups received 90-min air pressure exposures once daily for 5 days per week for a total of 8 weeks (total of 40 exposures). Staff at the participating hyperbaric medicine facilities knew the allocated treatment, but patients, clinicians, nurse practitioners, and other health-care professionals associated with patients' care were masked to treatment allocation. Primary endpoints were changes in the bowel component of the modified Inflammatory Bowel Disease Questionnaire (IBDQ) score and the IBDQ rectal bleeding score 12 months after start of treatment relative to baseline. The primary outcome was analysed in a modified intention-to-treat population, excluding patients who did not provide IBDQ scores within a predetermined time-frame. All patients have completed 12 months of follow-up and the final analysis is complete. The trial is registered with the ISRCTN registry, number ISRCTN86894066.
FINDINGS:
Between Aug 14, 2009, and Oct 23, 2012, 84 participants were randomly assigned: 55 to hyperbaric oxygen and 29 to sham control. 75 (89%) participants received 40 pressure exposures, all participants returned the IBDQ at baseline, 75 (89%) participants returned the IBDQ at 2 weeks post-treatment, and 79 (94%) participants returned the IBDQ at 12 months post-start of treatment. Patients were excluded from analyses of co-primary endpoints if they had missing IBDQ scores for intestinal function or rectal bleeding at baseline or at 12 months. In an analysis of 46 participants in the active treatment group and 23 participants in the control group, we found no significant differences in the change of IBDQ bowel component score (median change from baseline to 12 months of 4 (IQR -3 to 11) in the treatment group vs 4 (-6 to 9) in the sham group; Mann-Whitney U score 0·67, p=0·50). In an analysis of 29 participants in the active treatment group and 11 participants in the sham group with rectal bleeding at baseline, we also found no significant differences in the change of IBDQ rectal bleeding score (median change from baseline to 12 months of 3 [1 to 3] in the treatment group vs 1 [1 to 2] in the sham group; U score 1·69, p=0·092). Common adverse events in both groups were eye refractive changes (three [11%] of 28 patients in the control group vs 16 [30%] of 53 patients in the treatment group), increased fatigue (three [11%] vs two [4%]), and ear pain (six [21%] vs 15 [28%]). Eight serious adverse events were reported in eight patients: two were reported in two patients in the control group (tonsillitis requiring surgery [grade 3]; recurrent cancer of the vulva [grade 4]) and six serious adverse events were reported in six patients in the treatment group (malignant spinal cord compression requiring surgery [grade 3]; malignant paraortic lymph node involvement requiring surgery [grade 3]; recurrence of vomiting and dehydration [grade 3]; diarrhoea and fever associated with Campylobacter infection [grade 3]; recurrence of abdominal pain, bloating, diarrhoea, and urinary tract infection [grade 3]; aneurysm [grade 4]), none of which were deemed treatment-related.
INTERPRETATION:
We found no evidence that patients with radiation-induced chronic gastrointestinal symptoms, including those patients with rectal bleeding, benefit from hyperbaric oxygen therapy. These findings contrast with evidence used to justify current practices, and more level 1 evidence is urgently needed.
FUNDING:
Cancer Research UK and National Health Service (NHS) funding to the National Institute of Health Research Biomedical Research Centre at The Royal Marsden and the Institute of Cancer Research.

Cancer Radiother. 2016 Jun 21. pii: S1278-3218(16)30081-6. doi: 10.1016/j.canrad.2016.04.003. [Epub ahead of print]
[Hyperbaric oxygen and radiotherapy: From myth to reality].
[Article in French]

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Abstract
Worldwide, more than a million people receive each year a curative radiotherapy. While local control and overall survival are steadily increasing, 5 to 15% of patients still develop above grade 2 late toxicities. Late toxicities treatments are complex. Hyperbaric oxygenation was shown to induce revascularization and healing of injured tissues, but indications are still debated. Through a literature review, we summarized the hyperbaric oxygenation indications in radiation-induced late toxicities. We also studied the knowledge and practice of French local radiation therapists. It seems that hyperbaric oxygen therapy can be a conservative treatment of haemorrhagic cystitis and radiation-induced pain, in case of drug therapies failure. Often associated with a significant morbidity and mortality, surgery could be avoided. The risk of complications in case of tooth extraction in irradiated tissues is also reduced. However, the role of hyperbaric oxygenation for mandibular osteoradionecrosis, radiation-induced proctitis, enteritis, lymphoedema, brachial plexopathy, skin and neurological sequelae seems more questionable since studies results are conflicting. Future outcomes of phase III studies are expected to clarify the role of hyperbaric oxygenation in the management of radio-induced toxicities, including for head and necks complications.

Sci Transl Med. 2015 Mar 4;7(277):277ra30. doi: 10.1126/scitranslmed.aaa1260.
Immunological mechanisms of the antitumor effects of supplemental oxygenation
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Abstract
Antitumor T cells either avoid or are inhibited in hypoxic and extracellular adenosine-rich tumor microenvironments (TMEs) by A2A adenosine receptors. This may limit further

advances in cancer immunotherapy. There is a need for readily available and safe treatments that weaken the hypoxia-A2-adenosinergic immunosuppression in the TME. Recently, we reported that respiratory hyperoxia decreases intratumoral hypoxia and concentrations of extracellular adenosine. We show that it also reverses the hypoxia-adenosinergic immunosuppression in the TME. This, in turn, stimulates (i) enhanced intratumoral infiltration and reduced inhibition of endogenously developed or adoptively transfered tumor-reactive CD8 T cells, (ii) increased proinflammatory cytokines and decreased immunosuppressive molecules, such as transforming growth factor-β (TGF-β), (iii) weakened immunosuppression by regulatory T cells, and (iv) improved lung tumor regression and long-term survival in mice.
Respiratory hyperoxia also promoted the regression of spontaneous metastasis from orthotopically grown breast tumors. These effects are entirely T cell- and natural killer cell-dependent, thereby justifying the testing of supplemental oxygen as an immunological coadjuvant to combine with existing immunotherapies for cancer.

Cancer Res. 2014 May 15;74(10):2655-62. doi: 10.1158/0008-5472.CAN-13-3696. Epub 2014 Apr 28.
Releasing pressure in tumors: what do we know so far and where do we go from here? Hyperbaric Oxygen Therapy review
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Abstract
Tumor interstitial pressure is a fundamental feature of cancer biology. Elevation in tumor pressure affects the efficacy of cancer treatment. It causes heterogenous intratumoral distribution of drugs and macromolecules. It also causes the development of hypoxia within tumor bulk, leading to reduced efficacy of therapeutic drugs and radiotherapy.

Tumor pressure has been associated with increased metastatic potential and poor prognosis in some tumors. The formation of increased pressure in solid tumors is multifactorial. Factors known to affect tumor pressure include hyperpermeable tortuous tumor vasculatures, the lack of functional intratumoral lymphatic vessels, abnormal tumor microenvironment, and the solid stress exerted by proliferating tumor cells.

Reducing this pressure is known to enhance the uptake and homogenous distribution of many therapies. Pharmacologic and biologic agents have been shown to reduce tumor pressure. These include antiangiogenic therapy, vasodilatory agents, antilymphogenic therapy, and proteolytic enzymes. Physical manipulation has been shown to cause reduction in tumor pressure. These include irradiation, hyperbaric oxygen therapy, hyper- or hypothermic therapy, and photodynamic therapy. This review explores the methods to reduce tumor pressure that may open up new avenues in cancer treatment.

Undersea Hyperb Med. 2013 Jul-Aug;40(4):351-62.
Potential roles of hyperbaric oxygenation in the treatments of brain tumors
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Abstract
Over the past 50 years hyperbaric oxygen (HBO2) therapy has been used in a wide variety of medical conditions, and one of them is cancer. Many clinical studies have been conducted to evaluate potential therapeutic effects of HBO2 as a part of cancer treatment. This review briefly summaries the potential role of HBO2 therapy in the treatment of malignant tumors and radiation injury of the brain. HBO2 therapy is used for the enhancement of radiosensitivity in the treatment of some cancers, including malignant brain tumors. Radiotherapy within 15 minutes following HBO2 exposure, a relatively new treatment regimen, has been studied at several institutes and has demonstrated promising clinical results for malignant gliomas of the brain.
HBO2 therapy also increases sensitivity to some antineoplastic agents; non-randomized clinical trials using carboplatin-based chemotherapy combined with HBO2 show a significant advantage in survival for recurrent malignant gliomas.
The possibilities of combining HBO2 therapy with radiotherapy and/or chemotherapy to overcome newly diagnosed and recurrent malignant gliomas deserve extensive clinical trials. HBO2 therapy also shows promising potential for the treatment and/or prevention of radiation injury of the brain after stereotactic radiosurgery for brain lesions. The possibilities with HBO2 to enhance the therapeutic effect of irradiation per se, and to even increase the radiation dose if there are ways to combat the side effects, should boost new scientific interest into the whole field of oncology looking for new armamentaria to fight cancer.

Target Oncol. 2012 Dec;7(4):233-42. doi: 10.1007/s11523-012-0233-x. Epub 2012 Oct 2.
Hyperbaric oxygen therapy and cancer-a review - Hypoxia is a hallmark of solid tumors. Summary of the hypoxia-induced factors influencing cancer growth and progression
Source
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Abstract
Hypoxia is a critical hallmark of solid tumors and involves enhanced cell survival, angiogenesis, glycolytic metabolism, and metastasis.
Hyperbaric oxygen (HBO) treatment has for centuries been used to improve or cure disorders involving hypoxia and ischemia, by enhancing the amount of dissolved oxygen in the plasma and thereby increasing O(2) delivery to the tissue. Studies on HBO and cancer have up to recently focused on whether enhanced oxygen acts as a cancer promoter or not. As oxygen is believed to be required for all the major processes of wound healing, one feared that the effects of HBO would be applicable to cancer tissue as well and promote cancer growth. Furthermore, one also feared that exposing patients who had been treated for cancer, to HBO, would lead to recurrence. Nevertheless, two systematic reviews on HBO and cancer have concluded that the use of HBO in patients with malignancies is considered safe. To supplement the previous reviews, we have summarized the work performed on HBO and cancer in the period 2004-2012. Based on the present as well as previous reviews, there is no evidence indicating that HBO neither acts as a stimulator of tumor growth nor as an enhancer of recurrence.

- On the other hand, there is evidence that implies that HBO might have tumor-inhibitory effects in certain cancer subtypes, and we thus strongly believe that we need to expand our knowledge on the effect and the mechanisms behind tumor oxygenation.

Cancers (Basel). 2011 Jun 27;3(3):2811-26. doi: 10.3390/cancers3032811.
Tumor Necrosis Factor (TNF) and Chemokines in Colitis-Associated Cancer
Mukaida N, Sasakki S, Popivanova BK.
Source
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Abstract
The connection between inflammation and tumorigenesis has been well established, based on a great deal of supporting evidence obtained from epidemiological, pharmacological, and genetic studies. One representative example is inflammatory bowel disease, because it is an important risk factor for the development of colon cancer. Moreover, intratumoral infiltration of inflammatory cells suggests the involvement of inflammatory responses also in other forms of sporadic as well as heritable colon cancer.
Inflammatory responses and tumorigenesis activate similar sets of transcription factors such as NF-kB, Stat3, and hypoxia inducible factor and eventually enhances the expression of inflammatory cytokines including tumor necrosis factor (TNF) and chemokines.
The expression of TNF and chemokines is aberrantly expressed in a mouse model of colitis-associated carcinogenesis as well as in inflammatory bowel disease and colon cancer in humans. Here, after summarizing the presumed actions of TNF and chemokines in tumor biology, we will discuss the potential roles of TNF and chemokines in chronic inflammation-associated colon cancer in mice.

PLoS One. 2013 Nov 11;8(11):e78728. doi: 10.1371/journal.pone.0078728. eCollection 2013.
NF-κB-induced IL-6 ensures STAT3 activation and tumor aggressiveness in glioblastoma
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Abstract
Glioblastoma (GBM) is the most aggressive, neurologically destructive and deadly tumor of the central nervous system (CNS). In GBM, the transcription factors NF-κB and STAT3 are aberrantly activated and associated with tumor cell proliferation, survival, invasion and chemoresistance.
In addition, common activators of NF-κB and STAT3, including TNF-α and IL-6, respectively, are abundantly expressed in GBM tumors. Herein, we sought to elucidate the signaling crosstalk that occurs between the NF-κB and STAT3 pathways in GBM tumors. Using cultured GBM cell lines as well as primary human GBM xenografts, we elucidated the signaling crosstalk between the NF-κB and STAT3 pathways utilizing approaches that either a) reduce NF-κB p65 expression, b) inhibit NF-κB activation, c) interfere with IL-6 signaling, or d) inhibit STAT3 activation. Using the clinically relevant human GBM xenograft model, we assessed the efficacy of inhibiting NF-κB and/or STAT3 alone or in combination in mice bearing intracranial xenograft tumors in vivo.
We demonstrate that TNF-α-induced activation of NF-κB is sufficient to induce IL-6 expression, activate STAT3, and elevate STAT3 target gene expression in GBM cell lines and human GBM xenografts in vitro. Moreover, the combined inhibition of NF-κB and STAT3

signaling significantly increases survival of mice bearing intracranial tumors. We propose that in GBM, the activation of NF-κB ensures subsequent STAT3 activation through the expression of IL-6. These data verify that pharmacological interventions to effectively inhibit the activity of both NF-κB and STAT3 transcription factors must be used in order to reduce glioma size and aggressiveness.

Int J Clin Oncol. 2013 Mar 5. [Epub ahead of print]
Old but new methods in radiation oncology: hyperbaric oxygen therapy
Ogawa K, Kohshi K, Ishiuchi S, Matsushita M, Yoshimi N, Murayama S.
Source
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Abstract
The presence of hypoxic tumor cells is widely regarded as one of the main reasons behind the failure to control malignant tumors with radiotherapy treatments. Since hyperbaric oxygenation (HBO) improves the oxygen supply to the hypoxic tumor cells, HBO therapy has previously been used in combination with simultaneous radiotherapy to treat malignant tumors.
In some clinical trials, significant improvements in local control and survival have been seen in cancers of the head and neck and the uterine cervix. However, the delivery of simultaneous HBO therapy and radiotherapy is both complex and time-consuming, with some trials reporting increased side effects. As a result, the regimen of HBO therapy in combination with simultaneous radiotherapy has yet to be used as a standard treatment for malignant tumors. In recent years, however, radiotherapy immediately after HBO therapy has been emerging as an attractive approach for overcoming hypoxia in cancer treatment. Several studies have reported that radiotherapy immediately after HBO therapy was safe and seemed to be effective in patients with high-grade gliomas. Also, this approach may protect normal tissues from radiation injury. To accurately estimate whether the delivery of radiotherapy immediately after HBO therapy can be beneficial in patients with high-grade gliomas and other cancers, further prospective studies are warranted.

Br J Pharmacol. 2013 Feb;168(3):591-606. doi: 10.1111/bph.12008.
Interleukins in glioblastoma pathophysiology: implications for therapy
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Abstract
Despite considerable amount of research, the poor prognosis of patients diagnosed with glioblastoma multiforme (GBM) critically needs new drug development to improve clinical outcomes.
- The development of an inflammatory microenvironment has long been considered important in the initiation and progression of glioblastoma; however, the success of developing therapeutic approaches to target inflammation for GBM therapy has yet been limited.

Here, we summarize the accumulating evidence supporting a role for inflammation in the pathogenesis of glioblastoma, discuss anti-inflammatory targets that could be relevant for GBM treatment and provide a perspective on the challenges faced in the development of drugs that target GBM inflammation. In particular, we will review the function of IL-1β, IL-6 and IL-8 as well as the potential of kinase inhibitors targeting key players in inflammatory cell signalling cascades such as JAK, JNK and p38 MAPK