



CANCER/TUMOR LITERATURE

Urology. 2009 Jan;73(1):205-8. Epub 2008 Jun 25.

Effects of hyperbaric oxygen therapy on tumor growth in murine model of PC-3 prostate cancer cell line.

Tang H, Sun Y, Xu C, Zhou T, Gao X, Wang L.

OBJECTIVES: To test the hypothesis that hyperbaric oxygen (HBO) has no effect on tumor growth in a murine model of indolent in vivo prostate cancer. HBO means breathing pure (100%) oxygen under increased atmospheric pressure. **METHODS:** Human prostate PC-3 cells were injected into 40 severe combined-immunodeficient mice. They were randomized to undergo 20 sessions of either HBO or normobaric air in standardized conditions and observed for 4 weeks before histologic assessment of any palpable tumors that had developed. The analysis of the developed PC-3 tumors included tumor volume, microvessel density, apoptosis-associated markers (ie, p53, p27), and the proliferative index (Ki-67). **RESULTS:** The exposure to HBO at 2 atm for 20 treatment sessions, which comprised a daily 90-minute session, 5 d/wk, had no effect on the prostate cancer volume ($P > .05$). No differences were observed in tumor microvessel density, proliferative index, or apoptosis markers compared with the non-HBO group ($P > .05$). **CONCLUSIONS:** HBO did not have a tumor stimulatory effect on prostate cancer and could potentially be used safely in conjunction with other therapeutic modalities.

Int J Hyperthermia. 2009 Mar;25(2):160-7.

Systemic chemotherapy using paclitaxel and carboplatin plus regional hyperthermia and hyperbaric oxygen treatment for non-small cell lung cancer with multiple pulmonary metastases: Preliminary results.

Ohguri T, Imada H, Narisada H, Yahara K, Morioka T, Nakano K, Miyaguni Y, Korogi Y.

Purpose: The purpose of this retrospective case series was to evaluate the toxicity and efficacy of systemic chemotherapy using paclitaxel and carboplatin plus regional hyperthermia (HT) and hyperbaric oxygen treatment (HBO) for non-small-cell lung cancer (NSCLC). **Materials and methods:** Twenty-two patients with NSCLC with multiple pulmonary metastases intravenously received paclitaxel (50 mg/m²), carboplatin (area under the curve of 1.0-1.5) and 10% glucose weekly for 3 out of 4 weeks. Hyperthermia (HT) of the whole thoracic region was also administered weekly during intravenous infusion of carboplatin in all patients. In addition, 16 (72%) of 22 patients received hyperbaric oxygen (HBO) treatment immediately after weekly chemotherapy. A total of 107 cycles were performed in 16 patients with HBO, and 27 cycles in 6 patients without HBO. The toxicity and efficacy of these patients were retrospectively analyzed. **Results:** Both the hematologic and non-hematologic toxicities were mild and leucopenia/neutropenia of \geq grade 3 was seen in one patient, while pneumonitis of \geq grade 3 occurred in one patient. Fourteen (64%) of 22 patients had an objective response. The median time to progression of disease in all patients was 8 months and in 16 patients with HBO was 9 months. Four (44%) of 9 patients with prior chemotherapy including paclitaxel and carboplatin obtained objective responses. **Conclusions:** The novel combined therapy of paclitaxel and carboplatin with HT and HBO may therefore be a feasible and promising modality for treating NSCLC with multiple pulmonary metastases, and the results justify further evaluation to clarify the benefits of this treatment regimen.

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Cancer Treat Rev. 2008 Nov;34(7):577-91. Epub 2008 Jul 21.

Comment on: Hyperbaric oxygenation for tumour sensitisation to radiotherapy: a systematic review of randomised controlled trials.

Bennett M, Feldmeier J, Smee R, Milross C.

BACKGROUND: Radiotherapy is a well-established treatment for some solid tumours. Hyperbaric oxygenation (HBO) may improve radiotherapeutic killing of hypoxic cancer cells, so the simultaneous administration of radiotherapy and HBO may reduce mortality and tumour recurrence. METHODS: We performed a systematic search of the literature in September 2007 for randomised controlled trials, and made pooled analyses of pre-determined clinical outcomes. RESULTS: Nineteen trials contributed to this review (2286 patients). There was a reduction in mortality for head and neck cancers at one and five years after therapy (at five years RR 0.82, P=0.03, NNT=5), and improved local tumour control at three months (RR 0.58, P=0.006, NNT=7). Any advantage is achieved at the cost of an increased rate of both severe radiation tissue injury (RR 2.35, P<0.0001, NNH=8) and the chance of seizures during therapy (RR 6.76, P=0.03, NNH=22). CONCLUSIONS: There is some evidence that HBO improves local tumour control and mortality for cancers of the head and neck, and local tumour recurrence in cancers of the uterine cervix. These benefits may only occur with unusual fractionation schemes. HBO is associated with significant adverse effects including oxygen toxic seizures and severe radiation tissue injury. The methodological and reporting inadequacies of the studies included in this review demand a cautious interpretation. More research is needed for head, neck and uterine cervical cancer, but is probably not justified for bladder cancer. There is little evidence available concerning malignancies at other sites.

J Neurooncol. 2007 Nov;85(2):191-202. Epub 2007 Jun 8.

Hyperoxia retards growth and induces apoptosis, changes in vascular density and gene expression in transplanted gliomas in nude rats.

Stuhr LE, Raa A, Oyan AM, Kalland KH, Sakariassen PO, Petersen K, Bjerkvig R, Reed RK.

This study describes the biological effects of hyperoxic treatment on BT4C rat glioma xenografts in vivo with special reference to tumor growth, angiogenesis, apoptosis, general morphology and gene expression parameters. One group of tumor bearing animals was exposed to normobaric hyperoxia (1 bar, pO₂ = 1.0) and another group was exposed to hyperbaric hyperoxia (2 bar, pO₂ = 2.0), whereas animals housed under normal atmosphere (1 bar, pO₂ = 0.2) served as controls. All treatments were performed at day 1, 4 and 7 for 90 min. Treatment effects were determined by assessment of tumor growth, vascular morphology (immunostaining for von Willebrand factor), apoptosis by TUNEL staining and cell proliferation by Ki67 staining. Moreover, gene expression profiles were obtained and verified by real time quantitative PCR. Hyperoxic treatment caused a approximately 60% reduction in tumor growth compared to the control group after 9 days (p < 0.01). Light microscopy showed that the tumors exposed to hyperoxia contained large "empty spaces" within the tumor mass. Moreover, hyperoxia induced a significant increase in the fraction of apoptotic cells (approximately 21%), with no significant change in cell proliferation. After 2 bar treatment, the mean vascular density was reduced in the central parts of the tumors compared to the control and 1 bar group. The vessel diameters were significantly reduced (11-24%) in both parts of the tumor tissue. Evidence of induced cell death and reduced angiogenesis was reflected by gene expression analyses. Increased pO₂-levels in experimental gliomas, using normobaric and moderate hyperbaric oxygen therapy, caused a significant reduction in tumor growth. This process is characterized by enhanced cell death, reduced vascular density and changes in gene expression corresponding to these effects.

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Eur J Cancer. 2006 Dec;42(18):3304-11. Epub 2006 Sep 28.

The effect of hyperbaric oxygen therapy on tumour growth in a mouse model of colorectal cancer liver metastases.

Daruwalla J, Christophi C.

BACKGROUND AND AIMS: Hyperbaric oxygen (HBO) therapy involves the administration of 100% oxygen at high pressure. It has been used to treat a variety of conditions including non-healing wounds, carbon monoxide poisoning, and as an adjuvant to radiotherapy or chemotherapy. The effect of HBO alone on the growth of malignancy remains controversial. This study investigates the impact of HBO on tumour growth, kinetics and microcirculation of colorectal cancer liver metastases in an experimental model. METHODS: Male CBA mice were induced with colorectal liver metastases via an intrasplenic injection of a murine derived colorectal cell line. Tumours were examined using quantitative stereological analysis, histology and scanning electron microscopy of microvascular resin casts. The effect of HBO on tumour proliferation and apoptosis was quantified using immunohistochemistry. RESULTS: Daily exposure to HBO at 2.4 atm for 90 min had no effect on the volume of liver metastases. At day 13, HBO caused a significant reduction in tumour necrosis and proliferation compared to the non-HBO group ($p=0.002$ and $p=0.008$, respectively). By day 25 however, no differences were observed ($p>0.05$). No differences in apoptosis or microvascular architecture were observed. CONCLUSION: HBO did not have a tumour stimulatory effect on colorectal liver metastases and may potentially be used safely in conjunction with other therapeutic treatment modalities.

Undersea Hyperb Med. 2007 Mar-Apr;34(2):83-90.

Lung metastatic load limitation with hyperbaric oxygen.

Haroon AT, Patel M, Al-Mehdi AB.

Despite some theoretical concern about cancer-enhancing effects of hyperbaric oxygen (HBO₂) therapy, it is frequently administered to cancer patients. We evaluated the growth of murine breast cancer cells in the lung after hyperbaric oxygen treatment in an experimental metastasis assay. Young nu/nu mice were injected intravenously with 3×10^3 4T1-GFP tumor cells per g body weight followed by lung isolation, perfusion, and intact organ epifluorescence microscopy 1 to 37 days after injection. A group of animals ($n=32$) was exposed once daily for 5 days a week to 45 min of 2.8 ATA hyperbaric oxygen (HBO₂) in a research animal HBO₂ chamber. Control animals ($n=31$) were not subjected to HBO₂ treatment, but received similar intravenous administration of 3×10^3 4T1-GFP tumor cells. Single tumor cells and colonies were counted in the subpleural vessels in areas of about 0.5 cm² of lung surface. HBO₂ treatment did not lead to an increase in the number of the large or small colonies in the lungs. Rather, a significant reduction in the number of the large colonies was observed at 1 and 16 to 21-day periods of measurements after hyperbaric treatment. However, most importantly, there was a significant decrease in large colony size in the HBO₂ group during all periods of observation. The results indicate that HBO₂ is not prometastatic for breast cancer cells; rather it restricts the growth of large tumor cell colonies.



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World J Surg. 2006 Dec;30(12):2112-31.

Hyperbaric oxygen therapy for malignancy: a review.

Daruwalla J, Christophi C.

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 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.



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Int J Radiat Oncol Biol Phys. 2005 Sep 1;63(1):25-36.

Anemia, tumor hypoxemia, and the cancer patient.

Varlotto J, Stevenson MA.

PURPOSE: To review the impact of anemia/tumor hypoxemia on the quality of life and survival in cancer patients, and to assess the problems associated with the correction of this difficulty. **METHODS:** MEDLINE searches were performed to find relevant literature regarding anemia and/or tumor hypoxia in cancer patients. Articles were evaluated in order to assess the epidemiology, adverse patient effects, anemia correction guidelines, and mechanisms of hypoxia-induced cancer cell growth and/or therapeutic resistance. Past and current clinical studies of radiosensitization via tumor oxygenation/hypoxic cell sensitization were reviewed. All clinical studies using multi-variate analysis were analyzed to show whether or not anemia and/or tumor hypoxemia affected tumor control and patient survival. Articles dealing with the correction of anemia via transfusion and/or erythropoietin were reviewed in order to show the impact of the rectification on the quality of life and survival of cancer patients. **RESULTS:** Approximately 40-64% of patients presenting for cancer therapy are anemic. The rate of anemia rises with the use of chemotherapy, radiotherapy, and hormonal therapy for prostate cancer. Anemia is associated with reductions both in quality of life and survival. Tumor hypoxemia has been hypothesized to lead to tumor growth and resistance to therapy because it leads to angiogenesis, genetic mutations, resistance to apoptosis, and a resistance to free radicals from chemotherapy and radiotherapy. Nineteen clinical studies of anemia and eight clinical studies of tumor hypoxemia were found that used multi-variate analysis to determine the effect of these conditions on the local control and/or survival of cancer patients. Despite differing definitions of anemia and hypoxemia, all studies have shown a correlation between low hemoglobin levels and/or higher amounts of tumor hypoxia with poorer prognosis. Radiosensitization through improvements in tumor oxygenation/hypoxic cell sensitization has met with limited success via the use of hyperbaric oxygen, electron-affinic radiosensitizers, and mitomycin. Improvements in tumor oxygenation via the use of carbogen and nicotinamide, RSR13, and tirapazamine have shown promising clinical results and are all currently being tested in Phase III trials. The National Comprehensive Cancer Network (NCCN) guidelines recommend transfusion or erythropoietin for symptomatic patients with a hemoglobin of 10-11 g/dl and state that erythropoietin should strongly be considered if hemoglobin falls to less than 10 g/dl. These recommendations were based on studies that revealed an improvement in the quality of life of cancer patients, but not patient survival with anemia correction. Phase III studies evaluating the correction of anemia via erythropoietin have shown mixed results with some studies reporting a decrease in patient survival despite an improvement in hemoglobin levels. Diverse functions of erythropoietin are reviewed, including its potential to inhibit apoptosis via the JAK2/STAT5/BCL-X pathway. Correction of anemia by the use of blood transfusions has also shown a decrement in patient survival, possibly through inflammatory and/or immunosuppressive pathways. **CONCLUSIONS:** Anemia is a prevalent condition associated with cancer and its therapies. Proper Phase III trials are necessary to find the best way to correct anemia for specific patients. Future studies of erythropoietin must evaluate the possible anti-apoptotic effects by directly assessing the tumor for erythropoietin receptors or the presence of the JAK2/STAT5/BCL-X pathway. Due to the ability of transfusions to cause immunosuppression, most probably through inflammatory pathways, it may be best to study the effects of transfusion with the prolonged use of anti-inflammatory medications.

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Head Neck. 2005 May;27(5):362-9.

Effects of hyperbaric oxygen exposure on experimental head and neck tumor growth, oxygenation, and vasculature.

Shi Y, Lee CS, Wu J, Koch CJ, Thom SR, Maity A, Bernhard EJ.

BACKGROUND: Hyperbaric oxygen (HBO₂) is used to promote healing in irradiated tissues, but concern persists about the possibility that it may promote residual tumor growth. METHODS: The tumor growth of SQ20B and Detroit 562 head and neck squamous cell carcinoma xenografts were studied after single-dose irradiation and 5x/week HBO₂ treatment at 2.4 atm absolute for 90 minutes. The effect of HBO₂ treatment on tumor hypoxia and vasculature was also examined by immunohistochemical analysis. RESULTS: HBO₂ treatment increased tumor oxygenation during the treatment interval but did not promote the growth of either irradiated or unirradiated tumors. No increase in tumor vascular endothelial growth factor expression or vascularization was detected.

CONCLUSIONS: This study found no evidence for persistent changes in tumor microenvironment or tumor growth promotion caused by hyperbaric oxygen exposure.

BJU Int. 2004 Dec; 94(9):1275-8

Hyperbaric oxygen does not accelerate latent in vivo prostate cancer: implications for the treatment of radiation-induced haemorrhagic cystitis.

Chong KT, Hampson NB, Bostwick DG, Vessella RL, Corman JM.

OBJECTIVE: To assess the effects of hyperbaric oxygen (HBO₂; often used to treat haemorrhagic cystitis, a known side-effect after radiation therapy for prostate cancer and with the potential to induce tumour angiogenesis and stimulate latent recurrence) on indolent in vivo prostate cancer in a murine model. MATERIALS AND METHODS: Human prostate LNCaP cells were injected into 60 severe combined-immunodeficient mice; of these 24 (40%) did not develop palpable tumours after 6 weeks. They were randomized to undergo 20 sessions of either HBO₂ or normobaric air in standardized conditions, and observed for another 4 weeks before the histological assessment of any palpable tumours that developed. Analysis of developed LNCaP tumours included tumour volume, microvessel density, MIB-1, p53, p27 and racemase staining intensity. RESULTS: HBO₂ was associated with less prostate tumour progression than normobaric air (P = 0.26). During HBO₂ therapy, 10 mice remained free of palpable tumours, compared with seven controls (P = 0.30). On evaluation during the 4 weeks after therapy, six mice treated with HBO₂ remained free of palpable tumours, vs eight of the controls (P = 0.17). There was tumour invasion and necrosis in a two of six and four of the HBO₂ group during and after therapy, respectively, vs five and seven of the controls. Tumour microvessel density, proliferative index, differentiation and apoptosis markers were similar in both groups.

CONCLUSIONS: HBO₂ does not accelerate the growth of indolent prostate cancer in a murine model, suggesting that it does not increase the risk of residual prostate cancer reactivation when it is used to manage radiation-induced haemorrhagic cystitis in patients treated by pelvic radiotherapy for prostate cancer.



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Undersea Hyperb Med. 2004 Summer;31(2):251-60.

The effect of hyperbaric oxygen on human oral cancer cells.

Sun TB, Chen RL, Hsu YH.

Discoveries of the beneficial cellular and biochemical effects have strengthened the rationale for the administration of hyperbaric oxygen therapy (HBO2) as an adjunctive therapy for the treatment of osteoradionecrosis (ORN). Malignancies, however, are considered a contraindication for HBO2 because of the possible tumor-promoting effects. The aim of this study was to examine the effects of HBO2 therapy on tumor weight, and to measure the progression of apoptosis and tumor cell proliferating activity in a cultured human oral cancer cell line. Twenty 5-week-old male NODscid mice underwent daily HBO2 of 2.5 atm abs, 90 minutes for 20 treatments. The control group, n = 20, did not undergo HBO2 and tumor weight, apoptosis index, and proliferating activity parameters were compared between the two groups. The results showed no significant differences ($p < 0.05$) in the whole-body weights, tumor weights, apoptotic index or proliferating activity index between the two groups. **By using the apoptosis and proliferating activity assays which were better indicators of tumor cell growth than tumor weight alone, our results suggest that the clinical application of HBO2 does not promote the growth or proliferation of human oral cancer cells.**

Undersea Hyperb Med. 2003 Spring;30(1):1-18.

Hyperbaric oxygen: does it promote growth or recurrence of malignancy?

Feldmeier J, Carl U, Hartmann K, Sminia P.

It has been a concern that a therapeutic modality recommended as an adjunct to healing and administered to promote proliferation of fibroblasts, epithelial cells and blood vessels in a wound could also lead to proliferation of malignant cells and angiogenesis in a malignant tumor. The first reported concern that hyperbaric oxygen (HBO2) might have cancer growth enhancing effects appeared in a paper by Johnson and Lauchlan in 1966. In a series of patients treated with HBO2 radiosensitization, they reported a more frequent than expected incidence of metastases and an unusual pattern of metastases. The published literature from clinical reports, animal studies and cell culture studies are reviewed. Putative mechanisms whereby HBO2 could have carcinogenic effects are discussed. The processes of angiogenesis in wound healing and in cancer growth are compared and contrasted. **In vitro, in vivo and clinical studies strongly suggest no more than a neutral effect of HBO2 on tumor growth. In fact some studies suggest a negative impact of HBO2 on malignant progression or formation.** For angiogenesis, similarities in wound healing and cancer are striking but significant differences are found including the relative importance of angiogenic factors and the process of cessation of angiogenesis. Tumors that grow in hypoxic environments are more prone to metastases and more lethal to the patient. They are also more likely to mutate toward resistant genotypes. Discussion of postulated mechanisms of carcinogenesis including free radical and immunosuppressive effects points out why they are not likely to enhance or cause cancer growth or initiation. **In conclusion, the published literature on tumor angiogenesis mechanisms and other possible mechanisms of cancer causation or accelerated growth provides little basis for HBO2 to enhance malignant growth or metastases. A history of malignancy should not be considered a contraindication for HBO2 therapy.**



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In Vitro Cell Dev Biol Anim. 1999 Feb;35(2):98-101.

Exposure to hyperbaric oxygen induces cell cycle perturbation in prostate cancer cells.

Kalns JE, Piepmeier EH.

Cell cycle synchronization of tumor cells by exposure to hyperbaric oxygenation (HBO) may increase the efficacy of chemotherapy or radiation by placing cells into a chemosensitive portion of the cycle. The purpose of the current study was to examine oxygen pressure-dependent relationships with respect to the cell cycle in prostate tumor cells in vitro. LNCaP cells were grown in an incubator at 21% O₂ and then exposed to 100% oxygen at pressures up to 6 atmospheres (atm) for 1.5 h. Cells were then returned to the incubator and evaluated for DNA content by propidium iodide and new DNA synthesis with a pulse-chase experiment. Cell cycle effects were evaluated by flow cytometry. Exposure to HBO increased the percentage of cells synthesizing new DNA in a dose-dependent fashion: 0 atm, 44%; 6 atm, 65%. Cells that synthesize new DNA accumulate in G₂/M as a function of partial pressure of oxygen. These results suggest that HBO induces cells to enter the cell cycle and accumulate in G₂/M. Cell cycle synchronization and entry of senescent cells into the cell cycle suggest that HBO may be a useful adjuvant to chemotherapy or radiation in the treatment of prostate cancer. There are two potential mechanisms of action that may make HBO efficacious in the treatment of prostate cancer. HBO may potentiate cancer chemotherapeutic agents that cause damage to DNA during DNA synthesis or HBO may inhibit cell division causing accumulation in G₂/M.

Anticancer Res. 1998 Jan-Feb;18(1A):363-7.

The effect of hyperbaric oxygen on growth and chemosensitivity of metastatic prostate cancer.

Kalns J, Krock L, Piepmeier E Jr.

BACKGROUND: Currently, advanced prostate cancer (CaP) is not curable. In this report hyperbaric oxygen (HBO) is examined as an adjuvant to chemotherapy and as a stand-alone treatment. MATERIALS AND METHODS: CaP cell monolayers grown under normoxic conditions were exposed to cisplatin, taxol or doxorubicin for 90 minutes under HBO (3.0 atmospheres, 100% O₂) or normal pressure air. RESULTS: HBO reduced by 47% the concentration of doxorubicin required to produce a 20% reduction in cell numbers, but did not change the concentration required to produce a > 50% reduction. HBO increased the sensitivity of PC-3 cells to taxol at all concentrations, (mean 1.8%). Cisplatin chemosensitivity was not affected by HBO. HBO reduced the growth rate of DU-145 8.1% relative to control (p = 0.01), and PC-3 2.7% (p = 0.12). CONCLUSIONS: This study shows that HBO can decrease the rate of growth, and increase sensitivity to anticancer agents, however, the effects are cell line dependent.