© Med Sci Monit, 2005; 11(9): RA279-289
PMID: 16127374

Received: 2005.04.11
Accepted: 2005.06.21
Published: 2005.09.01

Hyperbaric oxygen and malignancies: a potential role in radiotherapy, chemotherapy, tumor surgery and phototherapy

Noori S. Al-Waili, Glenn J. Butler, Jorge Beale, Roger W. Hamilton, Bok Y. Lee, Paul Lucas

Life Support Technologies, Inc. and NewTechnologies, Inc, The Mount Vernon Hospital, Westchester Medical Center, New York Medical College, New York, U.S.A

Source of support: Self financing

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Summary

Over the past 40 years, hyperbaric oxygen (HBO_2) therapy has been recommended and used in a wide variety of medical conditions. In the 1950s, HBO_2 was first used as a treatment, in addition to radiation, for head and neck cancers and cervical cancer. Many studies have been conducted to investigate possible therapeutic effects HBO_2 as part of cancer management. Evidences showed that HBO_2 improved tumor oxygenation, and treatment with HBO_2 during irradiation has been shown to improve the radiation response of many solid tumors. It was used for delayed radiation injuries for soft tissue and bony injuries, for symptomatic radiation reactions of the urinary bladder and the bowel, for laryngeal radionecrosis, for radiation-induced optic neuropathy, for radiation-induced proctitis and for radiation-induced necrosis of the brain. HBO_2 also increases sensitivity to chemotherapy. A significant improvement in tumor response was obtained when photodynamic therapy (PDT) was delivered during hyperoxygenation. These studies were extensively reviewed and rational scientific basis for further investigations was discussed. The possibility of combining HBO_2, PDT and photosezitizers to overcome primary and secondary carcinoma deserve extensive laboratory and clinical research works. HBO_2 is a relatively benign with few contraindications, even for active cancer patients.

key words: **hyperbaric • oxygen • phototherapy • cancer • chemotherapy • hypoxia**

Full-text PDF: http://www.medscimonit.com/fulltxt.php?IDMAN=7332

Word count: 6711
Tables: 3
Figures: 2
References: 103

Author's address: Noori S AL-Waili, MD,PhD,DOG,CHT, Clinical Research Director, Life Support Technology and NewTechnology Groups, The Mount Vernon Hospital, Mount Vernon, NY 10550, U.S.A. e-mail: noori786@yahoo.com

BACKGROUND

HBO_2 means breathing pure (100%) oxygen under increased atmospheric pressure. HBO_2 induces high oxygen partial pressure in all tissues, reduces edema, causes activation of fibroblasts and macrophages, stimulates angioneogenesis and collage synthesis and has a bacteriostatic and bacteriocidic effect. HBO_2 chambers were developed at the turn of the 19th century to treat caisson workers and deep-sea divers who suffered from decompression sickness. Delivery of hyperbaric pressures is obtained through monoplace chambers which house one individual placed in the supine position. or multiplace chambers which can accommodate 2 to10 patients. HBO_2 is safe and complications are uncommon. Toxic effects of oxygen are observed at extremely high doses over prolonged periods. Central nervous system and pulmonary toxicity include mainly seizures, visual changes, sweating, muscle twitching, cough, pulmonary fibrosis and shortness of breath. Other potential complication is direct barotrauma such as middle ear injury [1].

The Undersea and Hyperbaric Medical Society has approved use of HBO_2 for several other conditions besides decompression sickness (Table 1). During the last decades, many laboratory and clinical studies reported that HBO_2 might help patients with arthritis, multiple sclerosis, cyanide poisoning, autism, stroke, chronic fatigue, allergy, cerebral palsy, senility, cirrhosis, and gastrointestinal ulcers (2, review).

DISEASE' TRIANGLE AND CANCER ETIOLOGY

Malignancy is a common challenging problem that leads to substantial amount of morbidity and mortality. In spite of early surgical interference, chemotherapy, radiotherapy and the advances in diagnostic tests that allow physician to detect cancer earlier complete cure remains a remote task. This is because the human body is being frustrated and exhausted by many factors including diet, environment and spiritual stress and human body misuse. These factors are called a triangle of disease (Figure 1), according to our new concept of illnesses [3,4]. Therefore, to control raising cancer incidence we have to modify and extent our options so as to include new therapies that include radical dealing with all items of disease's triangle for one side and to investigate role of natural and physical agents for therapy such as HBO_2, ultrasound, phototherapy, photosensitizers and electrotherapy as well as changing the life style [4].

CANCER AND HYPOXIA

Hypoxia is well known in tumors particularly solid tumors (Figure 2). The evidence for tumor hypoxia in human neoplasm was first reported in 1955. Since then, direct measurement by microelectrodes has revealed heterogeneity in intratumoural oxygen concentrations. Low oxygen concentrations are associated with poor local-regional control by radiotherapy. These findings coupled with the result of nuclear imaging studies provide evidence for the existence of tumor hypoxia which influences radiotherapy treatment outcome. Tumor hypoxia present in at least one third of cancers in the clinical setting [5]. Hypoxia of tumors exist due to restrictions in the oxygen delivery by perfusion and/or diffusion based on inadequate microcirculatory function, and in the oxygen transport due to tumor-associated anemia. Basically, both types of O_2 limitation coexist in solid tumors. We have proposed that tumor-associated anemia was attributed to tumor-induced prostaglandin production [6–10].

Generally, there is substantial evidence for the presence of hypoxia in human tumors. This is documented by histopathological demonstration of vascular insufficiency, direct oxygen measurements in tumors, and by physiological imaging and mapping of hypoxic areas. Hypoxia appears to be a problem in certain tumors such as squamous cell carcinoma. Hypoxia may occur in two principally different ways, viz acutely and chronically, yielding varying responses to modifying agents. Furthermore, it has been found that tumors that grow in hypoxic environments are more prone to metastases and more lethal to the patient. The tumors are also more likely to mutate toward resistant genotypes.

Hypoxia and compromised perfusion and metabolic changes that accompany hypoxia prompt resistance to chemotherapy. Moreover, it is well known that hypoxic cells are resistant to radiation. Tumor hypoxia is well recognized as a major factor contributing to radioresistance. The impact of cellular hypoxia on the growth, treatment and resistance of brain tumor, for example, has been recently reviewed [11].

Studies have focused on the hypoxia and sensitization of hypoxic cells in tumor for more than 30 years. Many interventions have been tried to overcome hypoxia (Table 2). Methods used to overcome hypoxia included the use of HBO_2, hypoxic cell radiosensitizers, and, more recently, modification of the oxygen-unloading capacity of haemoglobin [12]. Agents directed towards destruction of hypoxic cells have also been applied, such as hyperthermia and bioreductive drugs. Oxygen-mimetic radiosensitizers, adjuvant therapy with drugs that are preferentially toxic to hypoxic cells, using hyperthermia, or devising radiation were used to overcome the resistance induced by hypoxia. Past clinical studies have suggested that the outcome of therapy can be improved by many of these approaches, but none has yet produced a significant, and reproducible improvement in the therapeutic ratio [11].

Since the mid-1970s, clinical research in overcoming tumor hypoxia investigated the use of nitro-imidazoles as hypoxic cell sensitizers. Potential sensitizers with varying degrees of differential activity in tumor versus normal tissue are also discussed [13]. Hypoxic cytotoxins, such as tirapazamine, represent a novel approach in overcoming radioresistant hypoxic cells. However, the results from several clinical studies remain inconclusive. Only the use of HBO_2 has been shown as a beneficial adjunct to radiotherapy. Following the success of HBO_2 trials, a huge work was made to develop chemical agents which would mimic oxygen in their sensitization of hypoxic cells in solid tumors. The number of sites sensitized is limited to head, neck and cervix. The elimination of hypoxic cells is claimed by many as a worthy goal in radiobiology and many methods have been investigated in animal models [14]. These include: oxygen releasing chemicals, artificial oxygen carriers, inhibitors of oxygen consumption, and blood flow modifiers. HBO_2 or blood flow restriction has also been developed as

Table 1. The thirteen UHMS approved indications for hyperbaric oxygenation are listed (from the recently published 1999 UHMS Hyperbaric Oxygen Therapy Committee Report).

	Accepted indications for hyperbaric oxygen
1.	Air or gas embolism
2.	Carbon monoxide poisoning carbon monoxide complicated by cyanide poisoning
3.	Clostridial myositis and myonecrosis (gas gangrene)
4.	Crush injury, compartment syndrome, and other acute traumatic ischemias
5.	Decompression sickness
6.	Enhancement of healing in selected problem wounds
7.	Exceptional blood loss (anemia)
8.	Skin grafts and flaps (compromised)
9.	Necrotizing soft tissue infections
10.	Osteomeylitis (refractory)
11.	Delayed radiation injury (soft tissue and bony necrosis)
12.	Thermal burns
13.	Intracranial abscess

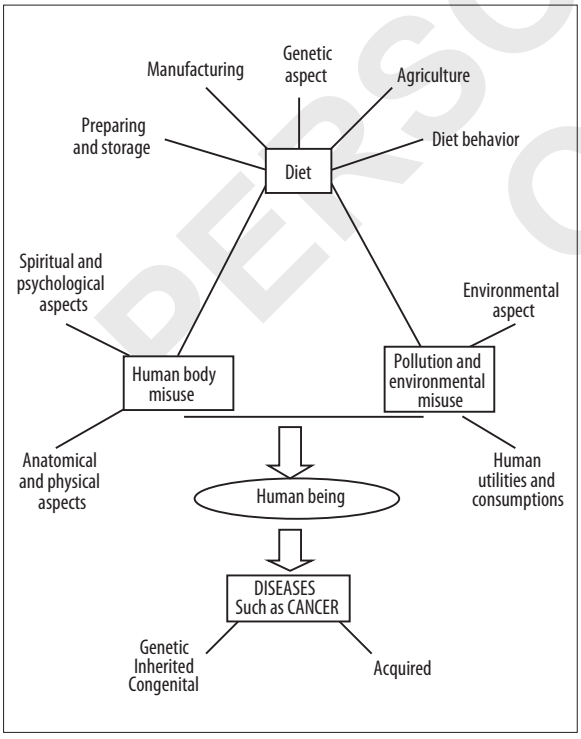

Figure 1. Al-Waili's diseases triangle (basic etiology of malignancies).

possible ways to modify radiation response through the radiochemical processes. Lee and his colleagues examined the role of hypoxia in influencing the treatment outcome following radiotherapy [15].

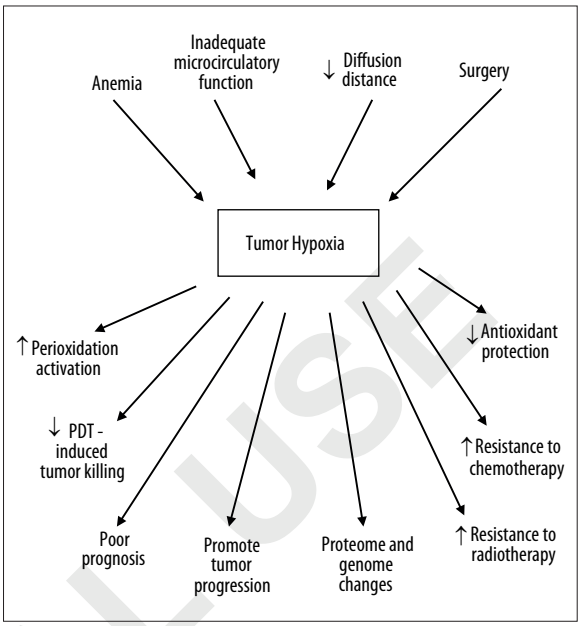

Figure 2. Causes and effects of tumor hypoxia.

Table 2. Methods to treating tumor hypoxia.

	Overcome hypoxia
1.	Hyperbaric oxygen
2.	Hypoxic cell radio-sensitization
3.	Modulation of oxygen unloading capacity of hemoglobin
4.	Blood flow modifiers
5.	Nicotanamide and carbogen
6.	Oxygen releasing substances
7.	Destruction of hypoxic cells by hypothermia and bio-reductive drugs

Hypoxia and Radiotherapy

Hypoxia is considered a major cause of failure of radiotherapy. The mechanisms of tumor hypoxia are still poorly understood. Therefore, effective ways for its correction or targeting are not obtained. Tumor vasculature is the way for the oxygen to reach the tumor stroma. Although anemia has long been focused on as an important parameter related to tumor hypoxia, differences in vascular density may also affect the intratumoral access of hemoglobin. Koukourakis et al., examined the vascular density in 1459 human carcinomas [16]. The vascular density was significantly higher in the tumor periphery as compared to inner areas.

Tumor hypoxia and anemia are known to adversely affect the efficacy of radiation therapy. Various treatment strategies aimed at increasing tumor oxygenation in head and neck cancer patients (including HBO_2 and hypoxic cell radiosensitizers) have been studied. The results showed that hypoxia adversely affects the radiosensitivity of cells.

In vitro studies with conventional photon radiation therapy under normoxic conditions have shown an effectiveness of 2.5-3.0 times greater than that achieved under anoxic conditions [17].

Hyperbaric Oxygen and Cancer Hypoxia

HBO_2 has been proposed to reduce tumor hypoxia by increasing the amount of dissolved oxygen in the plasma. Changes in tumor oxygenation induced by treatment with normobaric and HBO_2 and carbogen was studied [18]. R3230Ac mammary adenocarcinomas were implanted into Fisher 344 rats. They received normobaric 100% oxygen, hyperbaric (3 ATA) 100% oxygen, normobaric carbogen or hyperbaric (3 ATA) carbogen ± bretylium. Results demonstrated that normobaric oxygen and carbogen did not change tumor oxygenation significantly, but HBO_2 and hyperbaric carbogen improved tumor oxygenation.

HBO_2 has been shown to improve the radiation response of many solid tumors in rodents and in patients. Intravenous administration of perfluorochemical emulsions combined with oxygen breathing at atmospheric pressure has also been shown to improve the radiation response of tumors. The combination of a perfluorochemical emulsion and HBO_2 was tested by examining the radiation response of BA1112 rhabdomyosarcomas growing in WAG/rij-Y rats [19]. Treatment with a perfluorochemical emulsion, Fluosol-DA, plus HBO_2 (3 ATA) significantly increased the radiation response of the malignant cells in these solid tumors. In addition, the combination of Fluosol-DA and HBO_2 decreases the proportion of severely hypoxic cells in the tumor to less than 1.5% of the original value.

Hypoxia and surgical interference in patients with lung cancer is accompanied by peroxidation activation and decreased antioxidant protection. It was found that HBO_2 caused a decrease secondary peroxidation products content and mobilization of antioxidant activity. HBO_2 protected the cellular membrane from hypoxia-induced damages, and promoted a 1.5-fold reduction in the incidence of postoperative complications. It enhanced the efficacy of surgical treatment of patients with lung cancer [20]. A meta-analysis by Overgaard (1995) included 10703 cases entered into 83 randomized controlled trials has shown an overall improvement in local tumor control of 4.6% and in survival of 2.8% by hypoxic cell sensitization [21]. HBO_2 gave a 6.6% improvement in local control and hypoxic cell sensitizers. Since nicotinamide, the amide derivative of B3 is believed to prevent acute hypoxia, accelerated radiotherapy with carbogen and nicotinamide and hypoxic cytotoxins were introduced to overcome or improve tumor hypoxia [21,22].

In brain tumors, it was postulated that the resistance of gliomas to treatment with radiation and antineoplastic drugs might attributed in part to the effects of severe hypoxia presented in these tumors [11]. Hypoxic cells play a key role in the radioresistance of malignant glioma. Interferon-beta, nimustine hydrochloride and radiotherapy is a common therapy for malignant glioma in Japan. HBO_2 increases oxygen pressure in glioma tissue. Beppu, et al., Department of Neurosurgery, Iwate Medical University, Morioka, Japan applied radiotherapy after HBO_2 combined with interferon-beta and nimustine hydrochloride, for supratentorial malignant gliomas. The results suggested that this therapy could be applied to patients with poor prognostic factors [23].

Hyperbaric Oxygen and Anemia

Radiation therapy under hypoxic conditions is approximately one third as effective as that under normoxic conditions. Anemia is an important factor in the response of some human tumors to radiotherapy. The adverse effects of tumor hypoxia and anemia on the efficacy of radiation therapy have been recognized. The relationship between anemia and tumor response to radiation given in air or HBO_2 was examined in C3H mice transplanted with a mammary adenocarcinoma [24]. The tumor radiosensitivity was decreased when irradiation was given in air. This result suggested that tumors grown in anemic mice have a higher hypoxic fraction than those grown in healthy mice. Changes in host physiology with chronic anemia may contribute to the benefit seen with HBO_2.

There is clinical evidence of significantly reduced local-regional tumor control and overall survival in anemic patients receiving radiotherapy for head, neck, respiratory, pelvic, or genitourinary cancers [21]. It was observed that pretreatment hemoglobin level was significantly predictive of complete response at primary and nodal sites, local-regional failure-free survival, and overall survival by multivariate analyses [21].

Generally, recent studies have demonstrated the dramatic adverse impact of anemia upon tumor control. These studies have revealed hemoglobin levels as a powerful prognostic factor [22]. On the other hand**,** it was found that anemia produced an increase in radiosensitivity, which was further enhanced by red blood cell replacement. The most sensitive overall response was seen in the anemic-transfused group treated with HBO_2 [25].

Hyperbaric Oxygen and Cancer

HBO_2 and cancer growth

HBO_2 has been administered to promote proliferation of fibroblasts, epithelial cells and blood vessels in a wound; hence, it could also lead to proliferation of malignant cells. The published literature from clinical reports, animal studies and cell culture studies are reviewed [26]. The processes of angiogenesis in wound healing and in cancer growth are compared and contrasted. Some studies suggest a negative impact of HBO_2 on malignant progression or formation. The published literature on tumor angiogenesis mechanisms and other possible mechanisms of cancer pathogenesis or accelerated growth provides little basis for HBO_2 to enhance malignant growth or metastases. A history of malignancy should not be considered a contraindication for HBO_2 therapy [26]. By using the apoptosis and proliferating activity assays, recent study suggested that the clinical application of HBO_2 does not promote the growth or proliferation of human oral cancer cells [27]. HBO_2 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 [28].

HBO_2 has a tumor-suppressive effect during the induction phase of oral carcinoma and appears to have a stimulatory effect during the proliferative phase of carcinoma in the animal model [29]. HBO_2 was used as part of management of patients with glottis cancer. A retrospective analysis of 397 patients with glottic cancer, in which 240 patients were treated in air, and 157 patients in HBO_2 showed that the local tumor control rates explore a significant improvement in favor of HBO_2. The effects of HBO_2 on established squamous cell carcinoma were investigated [30]. Forty Golden Syrian hamster cheek-pouch carcinomas were induced with 9,10-dimethyl-1,2-benzanthracene. Twenty hamsters underwent 30 HBO_2 treatments for 60 min each to 2.81 ATA, while 20 served as controls. The results showed that animals receiving HBO_2 therapy had significantly smaller tumors and showed a fewer cervical metastases. HBO_2 therapy with coexistent carcinoma inhibited the established tumor's growth. The oxygen free radicals and malondialdehyde content in sarcoma tissues in the HBO_2 group was significantly higher than those of the control groups; necrosis incidence of sarcoma tissues and the survival rate of mice were higher; the time required for necrosis was shorter, and the volume and weight of sarcoma tissues were smaller and lighter than those of the control groups [31]. HBO_2 can accelerate the necrosis of S-180 sarcoma cells.

HBO_2 and tumor surgery

Surgical treatment under HBO_2 creates adequate conditions for such operations as oxygen saturation of the blood and tissues prevented hypoxia developing due to the severe operative trauma and blood loss. Intraoperative and early postoperative hemodynamic and gas exchange parameters become stable. To evaluate the effect of postoperative HBO_2 therapy on wound breakdown following radical vulvectomy, a prospective study was performed on patients undergoing radical vulvectomy at Scott and White Memorial Hospital, Temple, Texas [32]. HBO_2 therapy was initiated in the postoperative period. A significant difference was found comparing patients treated with lymph node dissections and HBO_2 to retrospective controls with lymph node dissections. Hospitalization was shorter in the HBO_2-treated patients. This study showed a reduction in wound breakdown for patients undergoing radical vulvectomy with lymph node dissections and HBO_2 therapy compared to similar patients not treated with HBO_2.

Regarding breast carcinoma, the persisting symptoms including pain, erythema, and edema after breast-conserving surgery and radiation are frequently reported. The use of HBO_2 was tested in symptomatic patients after breast cancer treatment [33]. Thirty women with persisting symptomatology after breast-conservation therapy received HBO_2 therapy in a multiplace chamber for a median of 25 sessions. HBO_2 therapy patients showed a significant reduction of pain, edema, and erythema scores as compared to untreated controls. Fibrosis and telangiectasia, however, were not significantly affected by HBO_2 therapy. It was concluded that HBO_2 therapy should be considered as a treatment option for patients with persisting symptomatology following breast-conserving therapy [33]. Moreover, it was found that using HBO_2 in operative treatment of renal carcinoma contributed to improvement of treatment outcome [34].

It was suggested that HBO_2 might improve radiation response by additional mechanisms separate from overcoming the oxygen effect [35]. It is well known that radiotherapy leads to cell tissue and vasculature damage. Surgery in such tissues has an increased complication rate because wound healing requires angiogenesis and fibroplasia as well as white blood cell activity, all of which are jeopardized. HBO_2 raises oxygen levels in hypoxic tissue, stimulates angiogenesis and fibroplasia, and has antibacterial effects.

Hyperbaric Oxygen and Chemotherapy

Resistance to chemotherapy is common in hypoxic tumors. HBO_2 may help overcome chemotherapy resistance by increasing both tumor perfusion and cellular sensitivity. In hypoxic tissues with symptomatic radiation reactions, HBO_2 induces the formation of collagen and angiogenesis resulting in permanently improved local microcirculation. HBO_2 causes tumor neovascularization in tumors of mice suncutaneously inoculated with cells from human epithelial ovarian cancer cell line [36]. There was significant tumor growth retardation in mice receiving both cisplatin and HBO_2 compared with those treated with cisplatin alone. Several reports indicate that it also increases sensitivity to alkylating agents. The effects of HBO_2 and 5-fluorouracil, individually and in combination, on sarcoma 180 implants in mice were investigated. It was found that in recipient animals concomitant HBO_2 increased accumulation of 5-flourouracil in the tumors, liver, and kidneys, but not in the brain. The results demonstrated that HBO_2 increases sensitivity to alkylating agents [37].

Other experiments were conducted to test the hypothesis that HBO_2 enhance the sensitivity of sarcoma cell line to doxorubicin (Adriamycin) in a rat model of pulmonary metastases [38]. Results demonstrated that HBO_2 plus doxorubicin produced significantly greater cytolysis of tumor cells than did doxorubicin alone. In addition, HBO_2 plus doxorubicin significantly decreased the number of lung metastases.

It is well documented that advanced prostate cancer is fatal and no curable measure is currently available. HBO_2 is examined as an adjuvant to chemotherapy [39]. Advanced prostate cancer cell monolayers grown under normoxic conditions were exposed to cisplatin, taxol or doxorubicin for 90 minutes under HBO (3 ATA) or normal pressure air. HBO_2 reduced by 47% the concentration of doxorubicin required to produce a 20% reduction in cell numbers, and increased the sensitivity of cells to taxol. Apparently, HBO_2 can decrease the rate of advanced prostate cancer cells growth, and increases their sensitivity to anticancer agents.

The effects of HBO_2 exposure on the cytotoxicity of Adriamycin and nitrogen mustard have been examined in Burkitt's lymphoma cells *in vitro* [40]. Exposure of cells to 3 ATA for 2 hr produces inhibition of DNA synthesis and mitosis. Cytotoxicity was increased when cells are exposed to HBO_2 during, before, or after exposure to nitrogen mustard. Simultaneous exposure to HBO_2 and adriamycin results in decreased cytotoxicity compared to drug treatment alone. HBO_2 produced an increase in adriamycin (0.15 microgram/ml) effects.

HYPERBARIC OXYGEN AND RADIOTHERAPY OF TUMORS

Tumor response

Radiotherapy has become one of the most important treatment modalities for human malignancy. Radiation therapy is often utilized as adjunctive or primary treatment for malignancies. Radiation complications are infrequent, but can be either life threatening or significantly diminish the quality of life. Radiotherapy after HBO_2 can be used to enhance the efficacy of clinical treatments. The treatment of delayed radiation injuries (soft tissue and bony radiation necrosis) by HBO_2 is one of many conditions approved by the UHMS. A systematic review of the 74 publications reporting the results of HBO_2 therapy in the treatment and/or prophylaxis of delayed radiation injury showed that all but seven of these publications report a positive result when HBO_2 is delivered as treatment for or prevention of delayed radiation injury [41]. It was found that without HBO_2 intervention, treatment often requires radical surgical approach with various complications. Based on this review, HBO_2 is recommended for delayed radiation injuries for soft tissue and bony injuries of most sites. In addition, there is evidences supporting HBO_2 for radiation-induced necrosis of the brain [41].

Of the 41 patients with delayed injuries of the abdomen and/or pelvis treated with HBO_2, 26 have healed; 6 failed to heal; and 9 patients had an inadequate course of therapy [42]. There were encouraging results with the resolution of fistulae in 6/8 patients. Moreover, it was found that success rate in patients receiving at least 20 HBO_2 treatments was 81%. Another study used HBO_2 in 27 patients with radiation-induced wounds, 9 of them underwent bony reconstruction of the mandible [43]. Results showed that HBO_2 is a very helpful tool in the management of problem-wound-healing, assisting the classical surgical principles. The effect of radiotherapy after HBO_2 in experimental tumors using a tumor growth delay assay was studied [44]. A significant growth delay in the treated animals within 30 min after HBO_2 was obtained, and the tumor growth delay time was prolonged 1.61 times as that in radiotherapy alone. It was concluded that radiotherapy after HBO_2 is effective for tumors with hypoxia. The time lapse from decompression to irradiation is an important factor in improving radiosensitivity.

HBO_2 improved local control and survival rates in patients with head and neck cancer receiving radiotherapy according to trials conducted early 1970s. Treatment with oxygent plus oxygen, carbogen (95% O2/ 5% CO_2), or HBO_2 increased the effects of radiation on the tumors [43]. This potentiation reflected an increase in the proportion of well-oxygenated tumor cells. The M.R.C. Working Party has coordinated randomized clinical trials to assess HBO_2 as a sensitizer in radiotherapy [46–48]. Between 1963 and 1976, 1669 patients were registered in these studies. HBO_2 significantly improved both survival and local tumor control after radiotherapy for both head and neck tumors and for advanced carcinoma of the cervix. In carcinoma of the bronchus there was some improvement in survival. The approach to radiosensitization has been evaluated in the treatment of 61 patients with bladder carcinoma using radical radiotherapy [49]. Patients receiving carbogen showed better response to radiotherapy. Hypothermia is associated with reduced metabolism of tissues and reduced oxygen consumption by tumors. If the blood supply to a hypothermic tumor can be maintained then the hypoxic fraction of cells should be reduced and consequently the radiation response would increase. It was reported that radiation under HBO_2 increased tumor response [50]. Four-day-old artificial pulmonary micrometastases of murine fibrosarcomas showed increased sensitivity to ionizing radiation by a factor of 1.13 when animals were exposed to oxygen breathing before and during irradiation [51].

HBO2 AND RADIATION COMPLICATIONS

Pelvic organs

Long-term manifestations of adverse effects caused by pelvic radiotherapy include abscess and fistula formation, stricture, mucus discharge, urgency, tinesmus, diarrhea, increased risk of cancer, and most commonly, bleeding [52]. HBO_2 was found effective as nonsurgical ways to treat the mucosal complications. HBO_2 was used in the treatment of radiation cystitis and proctitis following irradiation of prostate cancer in 18 patients [53]. The patients underwent HBO_2 therapy in a multiplace chamber for a median of 26 sessions. Interestingly, HBO_2 treatment was effective to treat those patients with post-radiation morbidity when conventional treatment has failed, HBO_2 should not be delayed too long in patients with radiation cystitis beacuse improvement is hard to achieve in the case of extensive bladder shrinkage. A review of 15 randomized controlled clinical trials of HBO_2 in radiotherapy yielded three with highly significant benefit and six with useful margins not reaching statistical significance [54]. The studies concluded that HBO_2 is a useful adjunct in treatment of delayed radiation injuries of the pelvis and abdomen.

Clinically, patients with proctitis following radiation therapy for prostates cancer suffered from bleeding, diarrhoea, incontinence, and pain. In more than half of these patients, symptoms partially or completely resolved after HBO_2 treatment [55]. Radiation-induced proctitis is a difficult clinical problem to treat and will probably become more significant with increasing prostatic cancer. A male patient suffered from a severe hemorrhagic radiation proctitis showed gradually improvement with HBO_2 [56]. HBO_2 was used to treat 47 patients with pelvic area radiation reactions [57]. Rectal bleeding and hematuria were improved in 61% and 55% of the patients respectively, while bladder incontinence was improved in 46% of the patients.

Hyperbaric oxygen therapy and hemorrhagic cystitis

Radiation therapy has been widely used for genitourinary carcinoma. Radiation cystitis often presents as hemorrhagic cystitis, which is refractory to conventional treatment and it may threaten the patient's life. Hemorrhagic cystitis remains a major long-term sequels in 1 to 2% of patients undergoing radiation therapy as part of their management for pelvic malignancy. Generally, radiation cystitis with macroscopic hematuria has been a challenging clinical problem for physicians. Conventional treatments may decrease hematuria but there is no active intervention to control radiation-induced refractory hemorrhagic cystitis in terms of efficacy and adverse effects.

HBO_2 therapy has been shown to improve angiogenesis and promote healing in radiation-injured tissue, including the bladder. Mathews et al., described the treatment and long-term follow-up of a cohort of patients treated with HBO_2 for hemorrhagic cystitis [58]. Seventeen patients with hemorrhagic cystitis received HBO_2 following failure of standard therapy. Hematuria resolved completely in 11 of 17 patients (64%), and 2 had only residual microscopic hematuria. Early application of HBO_2 was associated with earlier resolution of hemorrhagic cystitis.

In another study, 20 female patients with hemorrhagic radiation cystitis were treated with HBO_2 at a pressure of 2.5 ATA [59]. After an average of 44 HBO_2 sessions, macroscopic hematuria was completely relieved in 16 patients (80%) and markedly decreased in 2 patients (10%). There was a significant decrease in hemorrhagic sites and telangiectasis of the bladder mucosa. One patient had urinary frequency and urgency without hematuria during her hospital stay. After 30 sessions of HBO_2 therapy, her symptoms subsided. Moreover, HBO_2 was used also to treat 40 patients with biopsy-proven radiation cystitis and severe haematuria [60]. The results revealed that hematuria either disappeared completely or improved in 37 patients. HBO_2 therapy was used on other 10 patients with radiation cystitis, consisting of 20 sessions (3 to 5 sessions a week) [61]. Hematuria subsided and subjective symptoms including urinary frequency improved in seven patients. Mucosal edema, redness, and capillary dilation were partially improved.

Head and neck

Published reports on the use of HBO_2 in the radiation therapy of head and neck cancer are reviewed [62]. HBO_2 is of clinical value in the control of medium sized head and neck tumors. It is also of value in the treatment of lymph node disease and when used with nitroimidazoles as a radiation sensitizer. Follow-up data at five years are reported for 24 patients with squamous cell carcinoma of the head and neck, included in a randomized prospective study of radiotherapy either in HBO_2 or in air [63]. Results showed a significant gain in local control and survival rate with the use of HBO_2. Fifteen patients with soft-tissue wounds without signs of healing after surgery in full-dose (64 Gy) irradiated head and neck regions were treated with HBO_2 and adjuvant therapy [64]. HBO_2 accelerated the healing process. The results supports the claim that HBO_2 therapy has a clinically significant effect on initiation and acceleration of healing processes in irradiated soft tissues. HBO_2 in combination with hypofractionated radiation therapy was tested in patients with locally advanced squamous cell carcinoma of the head and neck [65]. Forty-eight patients with locally advanced unresected squamous cell carcinoma were randomized to radiation delivered in air or radiation under HBO_2. The study demonstrates substantial improvements in response rate with the use of HBO_2.

Data are presented to indicate the value of HBO_2 in all stages of treatment of patients with irradiation complications following head and neck surgery [66]. Oxygen is used as an adjunct to appropriate surgery. By using the two modalities together, the salvage rate for osteoradionecrosis and its complications of orocutaneous fistula, pathological fractures, and severe bone losses can be increased. It may also be used prophylactically in patients with periodontal disease or teeth requiring extraction in a previously irradiated area. From the patient's point of view, pain relief is achieved, function is returned, and prognosis improves [65]. Electrotherapy and HBO_2 therapy have been used to treat patients with postsurgery and radiation sequelae. Thirty-seven patients with problems of reduced oral opening and range of head movement, soft tissue necrosis, osteoradionecrosis, and delayed wound healing were studied over a 3-year period [67]. Although healing and the quality of the soft tissues showed marked improvement there was no significant improvement in oral opening.

Radionecrosis of the larynx is a debilitating disease associated with pain, dysphagia, respiratory obstruction. Persistent poor wound healing can lead to death. Signs and symptoms of radionecrosis were ameliorated in 7 of 8 patients with advanced radionecrosis treated with HBO_2 therapy [68]. This result indicates that HBO_2 therapy is a useful treatment modality in the management of laryngeal radionecrosis. Narozny et al., described two cases of palatine tonsil carcinoma treated with surgery and subsequent radiation therapy which caused severe radionecrosis of the larynx, pharynx and oral cavity. HBO_2 therapy resulted in complete resolution of postradiation changes [69].

Nervous system

Four patients with radiation-induced optic neuropathies were treated with HBO_2 [70]. Two began HBO_2 within 72 hours after development of unilateral optic neuropathy. Both had return of visual function to baseline levels. The other two patients initiated treatment 2 to 6 weeks after visual loss; they had no significant improvement of vision. Twenty patients with anaplastic astrocytoma or glioblastoma multiforme were treated with Fluosol and HBO_2 at 3 ATA [71]. Patients were irradiated in an HBO_2 chamber with 600 cGy weekly fractions following Fluosol administration. The addition of Fluosol/HBO_2 did not increase the incidence of HBO_2 related toxicities. It seems that fluosol and HBO_2 can safely be used as an adjunct to radiation in the treatment of brain tumors.

Kohshi et al., from the Department of neurosurgery, School of Medicine, University of Occupational and Environmental Health, 2003, describe a 68-year-old man who underwent HBO_2 therapy to manage radiation necrosis of the brain [72]. Improvement was noted with the HBO_2 therapy. The efficacy of radiotherapy combined with HBO_2 in 29 patients with malignant glioma was investigated [73]. The patients with post-operative residual tumors were locally irradiated with nitrosourea-based chemotherapy. Fifteen patients were irradiated daily after HBO_2, and fourteen other patients were treated without HBO_2. In the HBO_2 group, 73% showed almost 50% tumor regression. All responders were irradiated within 15 min after decompression. In the non-HBO_2 group, four had 29% tumor regression. The median survivals in patients with and without HBO_2 were 24 and 12 months, respectively. It was concluded that irradiation after HBO_2 was a useful form of treatment for malignant gliomas, but irradiation should be administered immediately after decompression.

Ten patients with radiation induced necrosis of brain received HBO_2 treatment [74]. HBO_2 was comprised of 20–30

sessions at 2.0 to 2.4 ATA, for 90–120 minutes. Initial improvement or stabilization of symptoms and/or imaging findings was documented in all 10 patients studied and no severe HBO_2 toxicity was observed. HBO_2 may prove to be an important adjunct to surgery and steroid therapy for central nervous system radiation-induced necrosis. The effects of the combination of MIBG (a structural analogue of norepinephrine, used in its radio iodinated form for the diagnosis and therapy of neuroblastoma) and HBO_2 on the human neuroblastoma cell line SK-N-BE(2c) was studied [75]. It was found that exposure of the neuroblastoma cells to HBO_2 enhanced the effects of MIBG on cell proliferation, lipid peroxidation and energy metabolism of the cell line.

Gynecological tumors

Therapeutic effect of HBO_2 on radiation-induced soft tissue necrosis in patients who previously received treatment for a gynecologic malignancy was studied [76]. Fourteen patients with gynecologic malignancy whose necrotic wounds failed to heal after 3 months of conservative therapy underwent 15 courses of HBO_2 treatments. All patients with radiation necrosis of the vagina alone or in association with rectovaginal fistula showed complete resolution of their lesions with HBO_2. It has been shown that patients with carcinoma of cervix who were severely anemic prior to radiotherapy showed very poor local tumor control when conventionally treated after transfusion, but very good local tumor control when treated with HBO_2 [77].

HBO_2 with irradiation were used in the treatment of patients with carcinoma of the uterine cervix [78]. HBO_2 increases tumor radiosensitivity. The use of HBO_2 in 329 patients with advanced carcinoma of cervix resulted in improved local control and survival rate [79]. The benefit was greatest in patients under the age of 55 who presented with stage III disease. HBO_2 combined with radiotherapy increased rate of tumor damage and resulted in a decreased percentage of the recurrence [80]. Increase in the percentage of distant metastases was noted in irradiation under HBO_2 therapy.

Children

The management of radiation-related sequelae with HBO_2 in children has not been well studied. Ashamalla et al. 1996 reviewed the University of Pennsylvania experience and reports the results of their analysis [81]. Between 1989 and 1994, ten children who underwent radiation therapy for cancer were referred for HBO_2 therapy. It was found that the use of HBO_2 for children with radiation-induced bone and soft tissue complications is safe and results in few significant adverse effects. HBO_2 was considered of great value both in the prevention and treatment of radiation-related complications [81].

Hyperbaric Oxygen Therapy and Phototherapy

PDT is a new therapeutic approach for the treatment of malignant tumors. The U.S. Food and Drug Administration have approved it for the palliative treatment of advanced lung and esophageal cancer. PDT involves light activation of certain dyes (photosensitizers) that are taken up by the target tissue. This process requires molecular of oxygen. PDT utilizes light activated drugs for the treatment of a wide variety of malignancies. Photochemical activation of the photosensitizer in the tumor site generates highly toxic singlet oxygen and other reactive oxygen species that kill cancer cells [82–84].

The photochemical reaction of PDT depends on the presence of molecular oxygen. The efficiency of PDF is limited because of anoxic regions in tumor tissue and vascular shutdown. Therefore, the use of HBO_2, which increases the oxygen in tumor tissue, as well as the amount of singlet oxygen, may enhance the efficiency of PDF. It has been shown that the cytotoxicity of porphyrins and related substances is mediated mainly by singlet oxygen and that hypoxic cells are less affected by porphyrins and light.

The efficacy of PDT is affected by the tissue concentration of the photosensitizer drug, the absorption of light energy and the availability of oxygen in the tumor during light irradiation. It has been demonstrated that the availability of molecular oxygen during Photofrin-PDT has a profound effect on the treatment outcome [85–87]. Hypoxic cells are resistant to PDT treatment, and without oxygen, PDT will have no cell killing effect [88–90]. In addition, PDT induces acute hypoxia because of oxygen depletion during the photochemical reaction. Tumor hypoxia, either preexisting or as a result of oxygen depletion during PDT, can significantly reduce the effectiveness of PDT-induced cell killing. In this regard, studies have reported the use of normobaric or HBO_2 to overcome tissue hypoxia [91–95].

Subjecting animals to normobaric 100% oxygen breathing or HBO_2 oxygenates preexisting hypoxic regions, compensates for PDT-induced oxygen depletion, and resulting in improving tumor control [85,96]. Supplemental hyperoxygenation was used to overcome tumor hypoxia and improve tumor cell killing during Photofrin-PDT [95]. When PDT is combined with hyperoxygenation, the hypoxic condition was improved and the cell killing rate at various time points after PDT was significantly enhanced over that without hyperoxygenation. It was suggested that enhanced direct and indirect cell killing was associated with high-concentration oxygen breathing. This study further confirms earlier observation that when a PDT treatment is combined with hyperoxygenation it can be more effective in controlling hypoxic tumors [97]. Another study examined C3H mice with transplanted mammary carcinoma tumors that were injected with 12.5 mg/kg Photofrin, irradiated with 630 nm laser light 24 h later and were then subjected to either HBO_2 or normobaric oxygen [98]. The results show a significant improvement in tumor response when PDT was delivered during hyperoxygenation.

Forty patients with inoperable, advanced malignant bronchial tumor stenosis were studied [99]. Photosensitization was carried out using a hematoporphyrin-derivative 2 mg/kg bw 48 h prior to PDT. At 1 and 4 weeks after the treatment the patients felt a significant improvement of dyspnea and hemoptysis. A significant reduction of tumor stenosis was obtained after PDT/HBO_2. Twenty-three other patients with esophageal and cardia cancer were treated by PDT and 29 patients received PDT under HBO_2 at a pressure of 2ATA [100]. Improvement regarding dysphagia and stenosis-diameter were obtained in both treatments with no significant difference. The tumor length decreased in

Table 3. Some effects of hyperbaric oxygen intervention in tumor biology and treatment.

	Effects of hyperbaric oxygen
1.	Reduces tumor hypoxia by increasing the amount of dissolved oxygen in plasma
2.	Improves radiation response of solid tumor
3.	Decreases hypoxia-induced peroxidation process in tumor
4.	Prevents surgery-induced hypoxia and shorten hospitalization
5.	Reduces signs and symptoms observed after breast-surgery and radiation
6.	Improves treatment results for renal carcinomas when combined with surgery
7.	Improves significantly local tumor control rates in glottic cancer
8.	Overcomes chemotherapy resistance by increasing tumor perfusion and cellular sensitivity
9.	Increases prostatic cancer sensitivity to anticancer agent
10.	Decreases number of lung metastasis when used with chemotherapy
11.	Decreases chemotherapy cytotoxicity
12.	Prevents delayed radiation injury
13.	Increases tumor sensitivity to alkylating agent
14.	Is useful in the management of laryngeal radionecrosis, radiation induced hemorrhagic cystitis and proctitis
15.	Decreases of percentage of tumor recurrence after irradiation under HBO_2
16.	Is used prophylactically in cases of periodontal diseases or teeth extraction in a previously irradiated area
17.	Improves PDT tumor cell killing rate

both groups and showed a significant difference in favor of the PDT/HBO_2 group. The mean survival time for the PDT group was 8.7 months and for the PDT/HBO_2 group was 13.8 months. Thirty other patients with inoperable non-small cell bronchogenic carcinoma and endobronchial stenosis were treated by PDT, photosensitization with a hematoporphyrin-derivative 2 mg/kg BW 48 hours prior to PDT and HBO_2 [101]. A significant reduction of tumor stenosis was documented 1 and 4 weeks after PDT/HBO_2.

In another study including patients with esophageal cancer, photosensitization was carried out with a hematoporphyrin-derivate 2 mg/kg BW 48 h prior to PDT [102]. Thirty-one patients were treated by PDT alone and 44 patients received PDT under HBO_2. The dysphagia-score and tumor-length also decreased in both groups and showed a significant difference in favor of the PDT/HBO_2-group. The median overall survival for the PDT-group was 7 months and for the PDT/HBO_2-group 12 months. It seems that combined PDT/HBO_2 represents a new approach in the treatment of esophageal and cardia cancer that appears to have enhanced the efficiency of PDT [102].

The use of PDT under HBO_2 as compared with PDT under normobaric conditions were assessed in patients with advanced esophageal carcinoma [103]. Photosensitization in all patients was carried out using hematoporphyrine derivate (2 mg/kg body weight 48 hours prior to PDT). Of these patients, 14 were treated by PDT alone, and 17 patients received PDT under HBO_2 at a 2ATA. The tumor length decreased in both groups and showed a significant difference in favor of the PDT/HBO_2 group. The 12-month survival rate was 28.6% for the PDT group and 41.2% for the PDT/HBO_2 group.

Despite the promising results from earlier clinical trials of PDT, considerable additional work is needed to bring this new intervention into clinical practice.

Conclusions and Future Works

HBO_2 showed potential effects in various modalities of cancer interventions (Table 3). It was well known that tumors growing in hypoxic environments are more prone to metastases and more lethal to patients. HBO_2 was used following breast-conserving therapy and vulvectomy. HBO_2 was also successful in overcoming the increased radio-resistance associated with anemia. HBO_2 reduces the morbidity associated with re-irradiation. HBO_2 significantly improves both survival and local tumor control after radiotherapy for head-and-neck tumors and for advanced carcinoma of the cervix. HBO_2 not only increases tumor radio-sensitivity but it decreases percentage of the recurrence. It also increases sensitivity to alkylating agents.

HBO_2 should be considered in the treatment of radiation-induced proctitis. HBO_2 therapy may be an alternative in symptomatic radiation reactions of the urinary bladder and the bowel. HBO_2 is a safe, effective, and well-tolerated treatment for radiation-induced soft tissue necrosis. Radiation induced hemorrhagic cystitis that does not respond to standard regimens can be successfully treated with HBO_2. Research has shown HBO_2 is effective when used in addition to conventional therapy for the prevention and treatment of radionecrosis.

Combined PDT/HBO_2 was effective in the treatment of esophageal and cardia cancer, inoperable non-small cell bronchogenic carcinoma and endobronchial stenosis. It was concluded that combined PDT/HBO_2 represents a new, safe and technically feasible approach that enables rapid reduction of the endoluminal tumor load. Combining HBO_2, PDT and photosezitizers to overcome primary and secondary carcinoma deserve extensive laboratory and clinical research works.

Generally, current publications about HBO_2, radiotherapy, chemotherapy, PDT and cancer supports the need for randomized studies examining the efficacy of HBO_2 alone or in combination with radiotherapy, electrotherapy, ultrasound, PDT or photosenzitizers in the management of various types of cancer. We are not far from a time when new scientific evidence will increase the adjunctive use of HBO_2 in radiation oncology as both a radiotherapy sensitizer and as a mediator in soft tissue and osteoradionecrosis. This author research group is developing rationale and clinical trial protocols for the utilization of HBO_2, in combination with

modalities, in the treatment of Glioblastoma multiforme brain tumor and metastatic prostate cancer.

REFERENCES:

1. Neumeister M: Hyperbaric oxyen therapy. *http://www.emedicine.com/plastic/topic526.htm#target5*, 2004
2. AL-Waili N, Butler G, Beale J et al: Hyperbaric oxygen stroke and neuronal diseases. Advance Ther, 2005; (accepted)
3. AL-Waili N: Disease's triangle. ALSaha Wltab, 2002, 180, 22–25
4. Al-Waili N: Medicine of Balance and Diseases triangle: New concept and nomenclatures. FASEB Journal, 2003; 17: 1236
5. Kalns J, Krock L, Piepmeier E Jr: The effect of hyperbaric oxygen on growth and chemosensitivity of metastatic prostate cancer. Anticancer Res, 1998; 18: 363–67
6. AL-Waili N: Indomethacin in basal cell carcinoma. J Pak Med Assoc, 1989; 39: 134–36
7. AL-Waili N, AL-Azzawi H: Effect of prostaglandin E2 on serum iron after acute and chronic blood loss. Clin Exp Pharmacol Physiol, 1985; 12: 443–46
8. Al-Waili N, Al-Azzawi H, Al-Rawi Z: Treatment of advanced chorionic carcinoma by indomethacin and steroids. Saudi Med J, 1984; 5: 81
9. AL-Waili N, Al-Azzawi H, Al-Niami M: Bone marrow cellular elements and peripheral blood indices following acute hemorrhage and prostaglandin E2 treatment. Saudi Med J, 1983; 4: 236–43
10. Al-Azzawi H, Al-Waili N: Haemopoietic changes following chronic blood loss and PGE2 treatment. First Scientific Congress, College of Medicine, University of Baghdad, 1984; 109
11. Knisely J, Rockwell S, Knisely J: The importance of hypoxia in the brain tumor. Neuroimaging Clin N Amer, 2002; 12: S25–S35
12. Overgaard J: Sensitization of hypoxic tumour cells – clinical experience. Int J Radiat Biol, 1989; 56: 801–11
13. Phillips T, Wasserman T: Promise of radiosensitizers and radioprotectors in the treatment of human cancer Cancer Treat Rep, 1984; 68: 291–302
14. Hirst D: Oxygen delivery to tumors. Int J Radiat Oncol Biol Phys, 1986; 12: 1271–77
15. Lee D, Moini M, Giuliano J, Westra W: Hypoxic sensitizer and cytotoxin for head and neck cancer. Ann Acad Med Singapore. 1996; 25: 397–404
16. Koukourakis I, Giatromanolaki A, Sivridis E, Fezoulidis I: Cancer vascularization: implications in radiotherapy? Int J Radiat Oncol Biol Phys, 2000; 48: 545–53
17. Kumar P: Impact of anemia in patients with head and neck cancer. Oncologist, 2000; 5(Suppl.2): 13–18
18. Brizel D, Lin S, Johnson J et al: The mechanisms by which hyperbaric oxygen and carbogen improve tumour oxygenation. Br J Cancer, 1995; 72: 1120–24
19. Martin D, Porter E, Rockwell S, Fischer J: Enhancement of tumor radiation response by the combination of a perfluorochemical emulsion and hyperbaric oxygen. Int J Radiat Oncol Biol Phys, 1987; 13: 747–51
20. Nikolaeva E, Stepanenko E, Chubukhchiev G: The effect of hyperbaric oxygenation on the indices of lipid peroxidation in the blood of patients with lung cancer. Anesteziol Reanimatol, 1991; 23: 67–69
21. Kumar P: Tumor hypoxia and anemia: impact on the efficacy of radiation therapy. Semin Hematol, 2000; 37(4 Suppl.6): 4–8
22. Knight K, Wade S, Balducci L: Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med, 2004; 116(Suppl.7A): 11S–26S
23. 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
24. McCormack M, Nias A, Smith E: Chronic anaemia, hyperbaric oxygen and tumour radiosensitivity. Br J Radiol, 1990; 63: 752–59
25. Rojas A, Stewart F, Smith K et al: Effect of anemia on tumor radiosensitivity under normo and hyperbaric conditions. Int J Radiat Oncol Biol Phys, 1987; 13: 1681–89
26. Feldmeier J, Carl U, Hartmann K, Sminia P: Hyperbaric oxygen: does it promote growth or recurrence of malignancy? Undersea Hyperbar Med, 2003; 30: 1–18
27. Sun TB, Chen RL, Hsu YH: The effect of hyperbaric oxygen on human oral cancer cells. Undersea Hyperb Med, 2004; 31: 251–60
28. .Chong KT, Hampson NB, Bostwick DG et al: Hyperbaric oxygen does not accelerate latent *in vivo* prostate cancer: implications for the treatment of radiation-induced haemorrhagic cystitis. BJU Int, 2004; 94(9): 1275–78
29. McMillan T, Calhoun K, Mader J et al: The effect of hyperbaric oxygen therapy of oral mucosal carcinoma. Laryngoscope, 1989; 99: 241–44
30. McDonald K, Bradfield J, Kinsella J et al: Effect of hyperbaric oxygenation on existing oral mucosal carcinoma. Laryngoscope, 1996; 106: 957–59
31. Lian Q, Hang R, Yan HF et al: Effects of hyperbaric oxygen on S-180 sarcoma in mice. Undersea Hyperb Med, 1995; 22: 153–60
32. Reedy M, Capen C, Baker D et al: Hyperbaric oxygen therapy following radical vulvectomy: an adjunctive therapy to improve wound healing. Gynecol Oncol, 1994; 53: 13–16
33. Carl U, Feldmeier J, Schmitt G, Hartmann K: Hyperbaric oxygen therapy for late sequelae in women receiving radiation after breast-conserving surgery. Int J Radiat Oncol Biol Phys, 2001; 49: 1029–31
34. Vol'pian L, Aliaev IuG, Iushkov M: Results of surgical treatment of cancer of the kidney with high surgical risk under hyperbaric oxygenation. Sov Med, 1991; 3: 27–29
35. Brizel D, Hage W, Dodge R et al: Hyperbaric oxygen improves tumor radiation response significantly more than carbogen/nicotinamide. Radiat Res, 1997; 147: 715–20
36. Alagoz T, Buller R, Anderson B et al: Evaluation of hyperbaric oxygen as a chemosensitizer in the treatment of epithelial ovarian cancer in xenografts in mice. Cancer, 1995; 75: 2313–22
37. Takiguchi N, Saito N, Nunomura M et al: Use of 5-FU plus hyperbaric oxygen for treating malignant tumors: evaluation of antitumor effect and measurement of 5-FU in individual organs. Cancer Chemother Pharmacol, 2001; 47: 11–14
38. Petre P, Baciewicz F Jr, Tigan S, Spears J: Hyperbaric oxygen as a chemotherapy adjuvant in the treatment of metastatic lung tumors in a rat model. J Thorac Cardiovasc Surg, 2003; 125: 85–95; discussion 95
39. Kalns J, Krock L, Piepmeier E: The effect of hyperbaric oxygen on growth and chemosensitivity of metastatic prostate cancer. Anticancer Res, 1998; 18: 363–67
40. Wheeler R, Dirks J, Lunardi I, Nemiroff M: Effect of hyperbaric oxygen on the cytotoxicity of adriamycin and nitrogen mustard in cultured Burkitt's lymphoma cells. Cancer Res, 1979; 39: 370–75
41. Feldmeier J, Hampson N: A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. Undersea Hyperb Med, 2002; 29: 4–30
42. Feldmeier J, Heimbach R, Davolt D et al: Hyperbaric oxygen an adjunctive treatment for delayed radiation injuries of the abdomen and pelvis. Undersea Hyperb Med, 1996; 23: 205–13
43. Steckeler S, Botel U, Warninghoff V: Hyperbaric oxygen therapy – an adjuvant therapeutic procedure with problem cases in reconstructive bone surgery. Fortschr Kiefer Gesichtschir, 1994; 39: 164–67
44. Kunugita N, Kohshi K, Kinoshita Y et al: Radiotherapy after hyperbaric oxygenation improves radioresponse in experimental tumor models. Cancer Lett, 2001; 164: 149–54
45. Rockwell S, Kelley M, Irvin C et al: Preclinical evaluation of oxygent as an adjunct to radiotherapy. Biomater Artif Cells Immobilization Biotechnol, 1992; 20; 883–93
46. Dische S: Hyperbaric oxygen: the Medical Research Council trials and their clinical significance. Br J Radiol, 1978; 51: 888–94
47. Watson E, Halnan K, Dische S et al: Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the cervix. Br J Radiol, 1978; 51: 879–87
48. The M.R.C. Working Party: Radiotherapy and hyperbaric oxygen. Report of a Medical Research Council Working Party. Lancet, 1978; 2; 881–84
49. Hoskin P, Saunders M, Dische S: Hypoxic radiosensitizers in radical radiotherapy for patients with bladder carcinoma: hyperbaric oxygen, misonidazole, and accelerated radiotherapy, carbogen, and nicotinamide Cancer, 1999; 86: 1322–28
50. Nias A, Perry P, Photiou A: Modulating the oxygen tension in tumours by hypothermia and hyperbaric oxygen. J R Soc Med, 1988; 81: 633–36
51. Milas L, Hunter NM, Ito H et al: Increase in radiosensitivity of lung micrometastases by hyperbaric oxygen. Clin Exp Metastasis, 1985; 3: 21–27
52. Johnston M, Robertson G, Frizelle F: Management of late complications of pelvic radiation in the rectum and anus: a review. Dis Colon Rectum, 2003; 46: 247–59
53. Mayer R, Klemen H, Quehenberger F et al: Hyperbaric oxygen – an effective tool to treat radiation morbidity in prostate cancer. Radiother Oncol, 2001; 61: 151–56

54. Dische S: What have we learnt from hyperbaric oxygen? Radiother Oncol, 1991; 20(Suppl.1): 71–74
55. Woo T, Joseph D, Oxer H: Hyperbaric oxygen treatment for radiation proctitis. Int J Radiat Oncol Biol Phys, 1997; 38: 619–22
56. Charneau J, Bouachour G, Person B et al: Severe hemorrhagic radiation proctitis advancing to gradual cessation with hyperbaric oxygen. Dig Dis Sci, 1991; 36: 373–75
57. Aanderud L, Thorsen E, Brattebo G et al: Hyperbaric oxygen treatment for radiation reactions. Tidsskr Nor Laegeforen, 2000; 120: 1020–22
58. Mathews R, Rajan N, Josefson L et al: Hyperbaric oxygen therapy for radiation induced hemorrhagic cystitis. J Urol, 1999; 161: 435–37
59. Lee H, Liu C, Chiao C, Lin S: Hyperbaric oxygen therapy in hemorrhagic radiation cystitis: a report of 20 cases. Undersea Hyperb Med, 1994; 21: 321–27
60. Bevers R, Bakker D, Kurth K: Hyperbaric oxygen treatment for haemorrhagic radiation cystitis. Lancet, 1995; 346: 803–5
61. Miyazato T, Yusa T, Onaga T et al: [Hyperbaric oxygen therapy for radiation-induced hemorrhagic cystitis.] Nippon Hinyokika Gakkai Zasshi, 1998; 89: 552–56
62. Sealy R: Hyperbaric oxygen in the radiation treatment of head and neck cancers. Radiother Oncol, 1991; 20(Suppl.1): 75–79
63. Berry G, Dixon B, Ward A: The Leeds results for radiotherapy in HBO for carcinoma of the head and neck. Clin Radiol, 1979; 30: 591–92
64. Neovius E, Lind M, Lind F: Hyperbaric oxygen therapy for wound complications after surgery in the irradiated head and neck: a review of the literature and a report of 15 consecutive patients. Head Neck, 1997; 19: 315–22
65. Haffty B, Hurley R, Peters L: Radiation therapy with hyperbaric oxygen at 4 atmospheres pressure in the management of squamous cell carcinoma of the head and neck: results of a randomized clinical trial. Cancer J Sci Am, 1999; 5: 341–47
66. Myers R, Marx R: Use of hyperbaric oxygen in postradiation head and neck surgery. NCI Monogr, 1990: 151–57
67. King G, Scheetz J, Jacob R, Martin J: Electrotherapy and hyperbaric oxygen: promising treatments for postradiation complications. J Prosthet Dent, 1989; 62: 331–34
68. Ferguson B, Hudson W, Farmer J Jr: Hyperbaric oxygen therapy for laryngeal radionecrosis. Ann Otol Rhinol Laryngol, 1987; 96(1 Pt 1): 1–6
69. Narozny W, Sicko Z, Przewozny T et al: Hyperbaric oxygen therapy as a method of treatment of laryngeal and pharyngeal Radionecrosis. Otolaryngol Pol, 2001; 55: 57–60
70. Guy J, Schatz N: Hyperbaric oxygen in the treatment of radiation-induced optic neuropathy. Ophthalmology, 1986; 93: 1083–88
71. Dowling S, Fischer J, Rockwell S: Fluosol and hyperbaric oxygen as an adjunct to radiation therapy in the treatment of malignant gliomas: a pilot study. Biomater Artif Cells Immobilization Biotechnol, 1992; 20: 903–5
72. Kohshi K, Imada H, Nomoto S et al: Successful treatment of radiation-induced brain necrosis by hyperbaric oxygen therapy. J Neurol Sci, 2003; 209: 115–17
73. Kohshi K, Kinoshita Y, Imada H et al: Effects of radiotherapy after hyperbaric oxygenation on malignant gliomas. Br J Cancer, 1999; 80: 236–41
74. Chuba P, Aronin P, Bhambhani K et al: Hyperbaric oxygen therapy for radiation-induced brain injury in children. Cancer, 1997; 80: 2005–12
75. Cornelissen J, Van J, Van Kuilenburg A, Flzinga L: Hyperbaric oxygen enhances the effects of meta-iodobenzylguanidine (MIBG) on energy metabolism and lipid peroxidation in the human neuroblastoma cell line SK-N-BE(2C). Anticancer Res, 1997; 17: 259–64
76. Williams J Jr, Clarke D, Dennis W et al: The treatment of pelvic soft tissue radiation necrosis with hyperbaric oxygen. Am J Obstet Gynecol, 1992; 167: 412–15; discussion 415–16
77. Dische S, Anderson P, Sealy R, Watson E: Carcinoma of the cervix – anaemia, radiotherapy and hyperbaric oxygen. Br J Radiol, 1983; 56: 251–55
78. Grigsby P: Modification of the Radiation Response of Patients With Carcinoma of the Uterine Cervix. Cancer Control, 1999; 6: 343–51
79. Watson E, Halnan KE, Dische S et al: Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the cervix. Br J Radiol, 1978; 5: 879–87
80. Sergeev S, Dar'ialova S, Lavnikova G: Hyperbaric oxygenation in the preoperative radiotherapy of soft tissue sarcomas. Vopr Onkol, 1977; 23: 17–27
81. Ashamalla H, Thom S, Goldwein J: Hyperbaric oxygen therapy for the treatment of radiation-induced sequelae in children. The University of Pennsylvania experience. Cancer, 1996; 77: 2407–12
82. Dougherty, T, Gomer C, Henderson B et al: Photodynamic therapy. J Natl Cancer Inst, 1998; 90, 889–905
83. Dalla Via L, Marciani Magno S: Photochemotherapy in the treatment of cancer. Curr Med Chem, 2001; 8, 1405–18
84. Sibata CV, Colussi C, Oleinick L, Kinsella T: Photodynamic therapy in oncology. Expert Opin Pharmacother, 2001; 2: 917–27
85. Chen Q, Huang Z, Chen H et al: Improvement of tumor response by manipulation of tumor oxygenation during photodynamic therapy. Photochem Photobiol, 2002; 76: 197–203
86. Dong GC, Hu S, Zhao G et al: Experimental study on cytotoxic effects of hyperbaric oxygen and photodynamic therapy on mouse transplanted tumor. Chin Med J, 1987; 100: 697–702
87. Jirsa Jr M, Pouckova P, Dolezal J et al: Hyperbaric oxygen and photodynamic therapy in tumor bearing nude mice. Eur J Cancer, 1991; 27, 109–12
88. Henderson B, Fingar V: Relationship of tumor hypoxia and response to photodynamic treatment in an experimental mouse tumor. Cancer Res, 1987; 47, 3110–14
89. Herzog M, Moser J, Wagner B et al: Effects and hypoxia in photodynamic therapy. Int J Oral Maxillofac Surg, 1994; 23, 406–8
90. Fuchs J, Thiele J: The role of oxygen in cutaneous photodynamic therapy. Free Radic Biol Med 24, 835–47. Effects of fluence rate. Br J Cancer, 1998; 77: 1386–94
91. Maier A, Anegg U, Tomaselli F et al: Does hyperbaric oxygen enhance the effect of photodynamic therapy in patients with advanced esophageal carcinoma? A clinical pilot study. Endoscopy, 2000; 32: 42–48
92. Maier A, Anegg U, Fell B et al: Hyperbaric oxygen and photodynamic therapy in the treatment of advanced carcinoma of the cardia and the esophagus. Lasers Surg Med, 2000; 26: 308–15
93. Maier A, Anegg U, Fell B et al: Effect of photodynamic therapy in a multimodal approach for advanced carcinoma of the gastro-esophageal junction. Lasers Surg Med, 2000; 26: 461–66
94. Tomaselli, F, Maier A, Sankin O et al: Acute effects of combined photodynamic therapy and hyperbaric oxygenation in lung cancer – a clinical pilot study. Lasers Surg Med, 2000; 28: 399–403
95. Tomaselli F, Maier A, Pinter H et al: Photodynamic therapy enhanced by hyperbaric oxygen in acute endoluminal palliation of malignant bronchial stenosis (clinical pilot study in 40 patients). Eur J Cardiothorac Surg, 2001; 5: 549–54
96. Chen Q, Chen H, Murphy J et al: Oxygen effect of photodynamic therapy. Proc SIPE, 1997; 2972: 80–87
97. Huang Z, Chen Q, Shakil A et al: Hyperoxygenation enhances the tumor cell killing of photofrin-mediated photodynamic therapy. Photochem Photobiol, 2003; 78: 496–502
98. Chen Q, Huang Z, Chen H et al: Improvement of tumor response by manipulation of tumor oxygenation during photodynamic therapy. Photochem Photobiol, 2002; 76: 197–203
99. Tomaselli F, Maier A, Pinter H et al: Photodynamic therapy enhanced by hyperbaric oxygen in acute endoluminal palliation of malignant bronchial stenosis (clinical pilot study in 40 patients). Eur J Cardiothorac Surg, 2001; 19: 549–54
100. Maier A, Anegg U, Fell B et al: Hyperbaric oxygen and photodynamic therapy in the treatment of advanced carcinoma of the cardia and the esophagus. Lasers Surg Med, 2000; 26: 308–15
101. Tomaselli F, Maier A, Sankin O et al: Acute effects of combined photodynamic therapy and hyperbaric oxygenation in lung cancer – a clinical pilot study. Lasers Surg Med, 2001; 28: 399–403
102. Maier A, Tomaselli F, Anegg U et al: Combined photodynamic therapy and hyperbaric oxygenation in carcinoma of the esophagus and the esophago-gastric junction. Eur J Cardiothorac Surg, 2000; 18: 649–54; discussion 654
103. Maier A, Anegg U, Tomaselli F et al: Does hyperbaric oxygen enhance the effect of photodynamic therapy in patients with advanced esophageal carcinoma? A clinical pilot study. Endoscopy, 2000; 32: 42–48

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