SPUMS Annual Scientific Meeting 2007

Hyperbaric oxygenation in the patient with malignancy: friend or foe?

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Key words
Hyperbaric oxygen, malignancy, outcome, review

Abstract
(Macdonald HM. Hyperbaric oxygenation in the patient with malignancy: friend or foe? *Diving and Hyperbaric Medicine.* 2007; 37: 133-8.)

Background: Hyperbaric oxygen (HBO) affects angiogenesis and cellular regeneration and is used to revitalise irradiated tissue. Assuming similarity in pathophysiology it is believed that tumour growth can be stimulated by HBO, and overt or suspected malignancy is considered a contra-indication to HBO by referring specialties.
Objectives: To determine whether the existing evidence supports or refutes this concept and whether the level of evidence utilised affects current published results and conclusions.
Methods: The critical appraisal worksheet for Harm/Aetiology from the Oxford Centre for Evidence Based Medicine was applied to studies of evidence level 3b and above, where a comparison was made of outcomes of malignancy between groups where HBO was used and similar groups without such exposure. Numbers in the treatment arms of selected trials were combined for outcomes which were worse, unchanged or better than those of controls.
Results and Conclusion: Fourteen human trials contributed to the final review. 3,434 patients were represented of whom 1,713 were not subjected to HBO and 1,721 were subjected to HBO as part of either a radiosensitisation protocol or for recovery of late radiation treatment injury. In 195 patients (11.3%) outcomes were worse than controls, 483 patients (28.1%) no difference was detected and in 1,043 patients (60.6%) outcomes were better with HBO. Comparison with existing reviews revealed differences in results but no difference in the trends noted and supports the conclusion that the balance of evidence in the existing literature refutes the perception that HBO is a risk factor for the patient with malignancy.

Introduction

World Health Organization statistics for 2005 estimate that 10 million people are diagnosed with cancer every year.[1] Approximately 50% will receive radiotherapy and of these 50% will be long-term survivors. Radiotherapy injures normal tissue in the field of radiation. Though improvement follows the acute phase, serious radiation-induced complications, known as late radiation tissue injury (LRTI), will affect 5–15% of long-term survivors.[2] With LRTI, progressive reduction in microvascular density and increasing fibrosis result in cellular hypoxia and inability to sustain normal function. This hypoxic, hypovascular and hypocellular situation is exacerbated by infection, surgery or dental extraction and can progress to a critical point where tissue breaks down causing soft-tissue radionecrosis or osteoradionecrosis.[3]

Hyperbaric oxygen (HBO) affects angiogenesis and cellular regeneration and is used to revitalise irradiated tissue.[3] Assuming similarity in pathophysiology, it is believed that tumour growth can be stimulated by HBO, and overt or suspected malignancy is considered a contra-indication to HBO by some referring specialties.[4]

Prior to HBO, the management of LRTI has been less than effective.[5] Surgical or dental intervention in an irradiated area can precipitate disfigurement, poor healing and infection. HBO stimulates angiogenesis in an irradiated field. Typically the treatment regime involves pressures of 243 kPa (2.4 ATA) using 100% oxygen for 90 minutes for 30–40 (usually daily) treatments. Another regime is applied to reduce hypoxia in solid tumours prior to radiotherapy, which involves pressurisation to 202–405 kPa (2.0–4.0 ATA), breathing 100% oxygen for 20–30 minutes for pre-oxygenation, during or following which radiotherapy is delivered.

Radiosensitisation was designed to *decrease* tumour recurrence and metastasis. Concerns that HBO might have cancer-enhancing effects were published by Johnson and Lauchlan in 1966, generating animal and human trials to clarify the effect of HBO on tumour growth.[6] Due to the technical difficulties of combining HBO and radiotherapy, this approach has been largely abandoned despite promising results.

Though the purpose and regimen of HBO as a radiosensitiser differ from the treatment of LRTI, it remains important to consider whether HBO affected tumour recurrence and spread beneficially or adversely. Therefore the outcomes

recorded in these trials have been combined for the purposes of this study. Longer-term follow up of tumour growth was recorded in the trials for radiosensitisation. A challenge in the interpretation of data from treatment for LRTI is the lack of long-term follow-up data recording specifically the presence or absence of tumour recurrence/metastasis. An assumption has to be made, therefore, that if this was not recorded it did not occur. Though apparently a logical conclusion, given the seriousness of recurrence or metastasis, assumptions do not accord well with the scientific method and the tenets of evidence based medicine.[7]

A review by Feldmeier et al included published articles, text books and conference proceedings from 1966–1993 including human and animal data – evidence level 1 (randomised controlled trial) to 5 (case report).[8,9] He concluded that "*the published literature on tumour angiogenesis mechanisms and other possible mechanisms of cancer causation or accelerated growth provides little basis for hyperbaric oxygen to enhance malignant growth or metastases. A history of malignancy should not be considered a contra-indication for hyperbaric oxygen therapy.*"[8] Conclusions, no matter how valid, based on such heterogeneity of evidence should be questioned by practitioners in the disciplines for which this information is critical in terms of referrals. In contrast, two Cochrane reviews selected randomised and quasi-randomised controlled trials only.[10,11]

Whereas trials of drug therapy accommodate large numbers, narrow entry criteria and well-matched placebo controls, practical considerations around generating a valid placebo arm for HBO leads to trials of high-level evidence being much smaller. Surgical disciplines share the challenge of creating valid placebo arms and, in the effort to generate rigorous entry criteria, numbers in such trials are usually small. Meta-analysis of a series of trials with low individual power can lead to confusion about appropriate therapeutic decisions and is associated with the possibility of a Type II error.[7] A case can be made for the inclusion of cohort prospective (level 3) evidence in disciplines where the treatment modality is technical in nature and reviews represent either high numbers with uncritical inclusion, or few numbers with critical appraisal.

Objectives

Assessments were made of human studies from evidence level 3b and higher to answer the questions:

1 Does hyperbaric oxygen treatment pose risks to patients who have known or occult malignancy at the time of their treatment in terms of tumour activation or metastatic spread?
2 Does the evidence level utilised in a review affect trends and clinical conclusions already published?

Search strategy

The following search strategy was used, with an English-language restriction:

- Electronic searches (January 1966–June 2006) were undertaken of the Cochrane Library (CENTRAL Issue 3, 2005); MEDLINE; CINAHL; EMBASE and the database of randomised controlled trials in hyperbaric medicine (DORCTHIM).
- Hyperbaric textbooks and journals (*Undersea and Hyperbaric Medicine*, *South Pacific Underwater Medicine Society Journal* and *Aviation, Space and Environmental Medicine*)
- The reference lists of relevant articles were searched manually.

CRITERIA FOR INCLUSION OF STUDIES

The types of studies included were meta-analyses and reviews, randomised and quasi-randomised controlled trials, cohort and case-controlled studies. The participants and interventions chosen were diagnosed cancer patients with radiotherapy and treated with HBO, compared with similar regimens excluding HBO.

OUTCOME MEASURES

Studies were included if they reported *or were expected to report* the following outcome measures at any time:

- mortality rate
- local recurrence or growth rate
- metastatic disease occurrence or spread.

TRIAL IDENTIFICATION

Abstracts identified by the initial search were assessed and the full text of suitable articles retrieved electronically or from the libraries of the universities of Auckland and Otago or private collections of experts in the field.

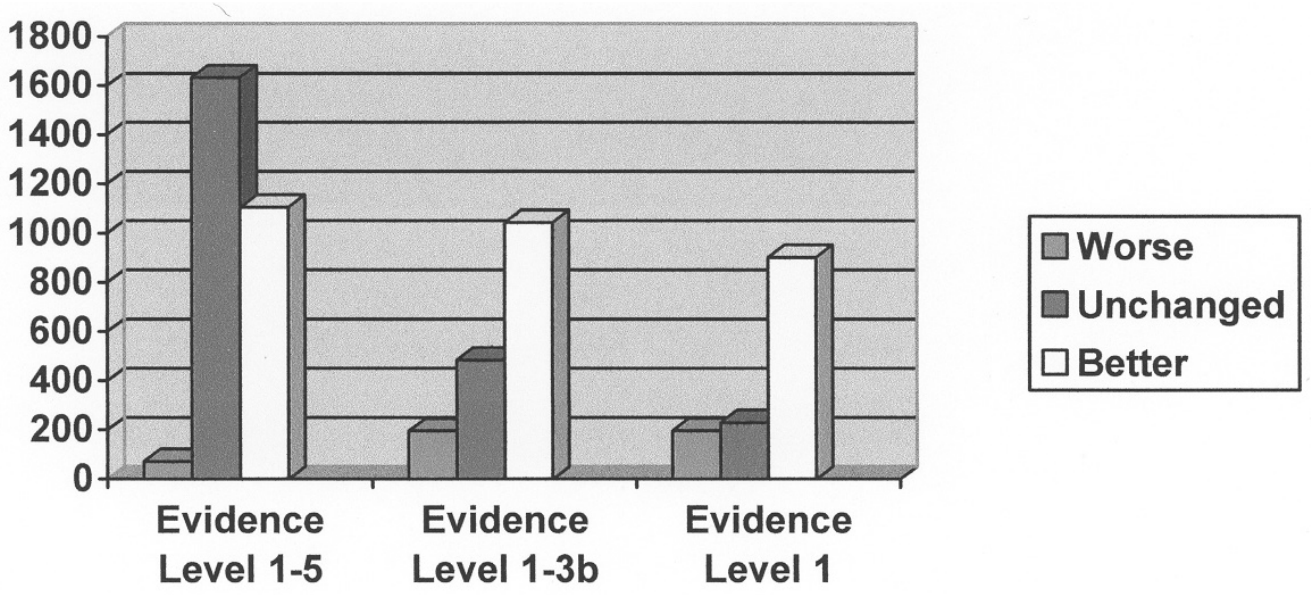
QUALITY ASSESSMENT

Study quality assessment utilised Schulz's method (1995).[12] The reference from a recent comprehensive review was included, giving the rationale for exclusion of duplicate trials.[13]

ANALYSES AND METHODOLOGICAL QUALITY OF INCLUDED STUDIES

The critical appraisal worksheet for Harm/Aetiology from the Oxford Centre for Evidence Based Medicine (EBM) was applied to studies of evidence level 3b and above, where a comparison was made of outcomes of malignancy between groups where HBO was used and similar groups without such exposure.[14] Numbers in the treatment arms of selected trials were combined for outcomes which were worse, unchanged or better than controls. This simple index

Figure 1
Comparison of the numbers of patients in three reviews of the effect of HBO on malignancy, based on different levels of evidence. Patients are categorised as worse off, unchanged or better off than control patients who did not receive HBO.[3,15–27]



outcome was chosen not (as was the original intention of the studies of radiosensitisation and treatment for LRTI) to determine whether HBO was beneficial, but to ascertain whether an adverse outcome in terms of malignancy had occurred that could be attributed to HBO as part of a treatment process.

Computation of risk ratio (RR), confidence interval (CI) and numbers needed to harm was not possible due to the heterogeneity of study types, malignancy types, anatomical sites and levels of evidence.[3,15–27] Whereas RR and CI have been calculated for each randomised controlled trial individually and are not repeated here,[10,11] the combined totals from all trials did not represent figures that could be analysed in this fashion. Data included case-controlled studies which can provide only prevalence of exposure and causation and an odds ratio cannot be calculated. The measure of risk obtained from a case-controlled study is an *estimate* of the RR only.[28] The original review by Feldmeier presented the same difficulties in statistical analysis and as one objective of this review was to provide comparative data, the same type of analysis would need to be applied to all those reviews being compared.

Because of the simplicity of the index endpoint the numbers from the various studies could be combined and percentages of the total calculated to provide comparative data, and histograms for graphic representation of trends. In order to establish whether a causal relationship could be assumed between HBO and changes in the behaviour of malignancy, the Bradford-Hill criteria of causation were applied.[29]

Results are portrayed as histograms from the Feldmeier, Cochrane and the present reviews as the actual numbers of patients combined, where HBO preceded outcomes that were:

- worse than those in the untreated group
- no different from those in the untreated group
- better than those in the untreated group (Figure 1).

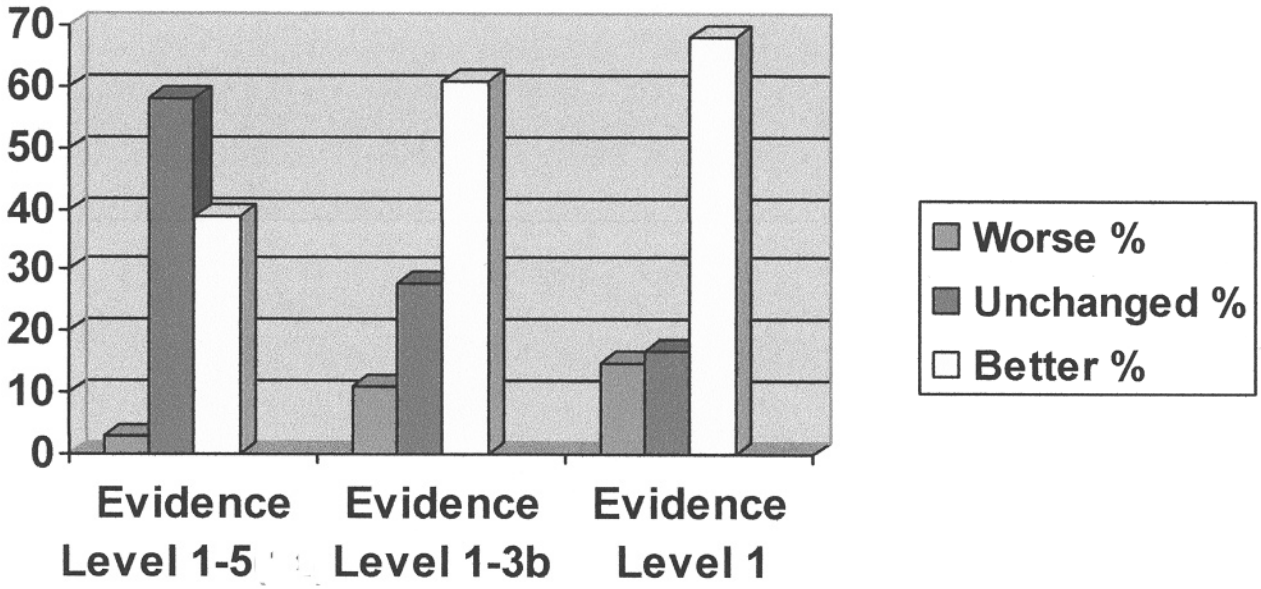
Results

Fourteen human trials from 1966 to July 2006, with level of evidence 1–3b and above contributed to the final review.[3,15–27] A total of 3,434 patients were represented of whom 1,713 were not subjected to HBO and 1,721 were subjected to HBO as part of a radiosensitisation protocol or for recovery of LRTI. Of the latter, 195 had outcomes worse than those of controls, in 483 no difference in outcomes was detected and in 1,043 the outcomes in the HBO group were better than those for controls (Figure 1).

In the review by Feldmeier,[8] combining all studies from 1966 to 1993, 2,808 patients underwent HBO. In 72 patients outcomes were worse with HBO than for controls, in 1,632 no difference in outcomes was seen and in 1,104 exposed to HBO improved long-term outcomes were seen compared to the control group (Figure 1).

Results from the Cochrane reviews,[10,11] from randomised and quasi-randomised controlled trials to 2004, showed that of 1,325 patients treated with HBO, in 195 the outcomes were worse than for controls, in 228 there was no demonstrable difference in outcomes and in 902 the outcome in the HBO group was better than in the control group (Figure 1).

Figure 2
Comparison of the percentage of patients (to allow normalisation of the data) in the three reviews of the effect of HBO on malignancy. Patients are categorised as worse off, unchanged or better off than control patients who did not receive HBO.[3,15–27]



A second graph represents the three outcome groups from the Feldmeier, Cochrane and present reviews expressed as percentages of the combined patient totals, providing a common denominator by which trends can be demonstrated (Figure 2).

Discussion

The use of HBO as an adjunct in head and neck surgery is well established and is increasing for treatment of other irradiated anatomical sites. Such patients usually undergo extensive surgical resections with disruption of vascular supply and resultant chronic hypoxic wounds, radionecrosis or fistula formation adding to the risk of infection. HBO stimulates leukocyte bactericidal activity, angiogenesis, fibroblast activity, and collagen formation creating a favourable environment for healing and resisting infection.[3] HBO in conjunction with radiotherapy has been studied since the 1950s on the assumption that tumour cell hypoxia directly influences radiation. Concern has been expressed over the possibility of increased risk of distant metastases with combination radiation therapy and HBO, whereas the balance of evidence appears to refute this concern.

In all three reviews represented above, where differing levels of evidence were included in each review, the numbers and percentages of patients having received HBO and being perceived as worse off remained in the minority, i.e., 2.6%, 11.3% and 14.7% respectively. It is noteworthy that the higher the level of evidence utilised, the more sensitive the data became to detect evidence of harm. This may reflect a potential positive publication bias particularly in literature of lower evidence level.

However, in terms of those patients perceived to be better off, the same trend to improved outcomes was evident the higher the level of evidence used, i.e., 39.3%, 60.6% and 68.1% respectively. The biggest difference was apparent in the percentages where no change was noted between the hyperbaric group and controls, i.e., 58.1%, 28.1% and 17.2% respectively.

No definite hypothesis can be invoked to account for this. Despite the reversal of trend in terms of 'no difference' to 'better off', the aim of the review remains to ascertain whether the balance of evidence confirms or refutes the perception of harm to patients undergoing HBO with overt or covert malignancy. In this respect the figures of no difference and improved outcomes can be combined as both represent a lack of harm to the patient. From Table 1 it would appear, therefore, that the balance of evidence refutes the perception of harm to the patient with malignancy.

Table 1
Relationship between the levels of evidence used in clinical reviews and the risk of cancer being worsened with HBO. The 'no harm' group combines studies reporting no difference in cancer rates and those with reduced rates in the HBO groups.

Level of evidence	Harm (% patients)	No harm (% patients)
1-5	2.6%	97.4%
1-3	11.3%	88.7%
1	14.7%	85.3%

The second point is that the level of evidence used in the various reviews, though differing in the actual percentages, maintains the same trend and conclusion through all levels. The closest correlation was between the higher levels of evidence. The comparison is not without bias, however, as the uncritical review utilised literature from 1966 to 1993 whereas the other reviews utilised literature from the same starting date, but ended at 2006 (the present study) and 2004 (Cochrane reviews) respectively. Literature that would have been included in the uncritical review had it covered similar dates, was identified and would have changed the figures and percentages to include more in the harm category though still without altering the trends and conclusion.[30]

Despite the weight of evidence in favour of no harm with HBO treatment to the patient with malignancy, the fact that concerns have been raised, and that some outcomes are documented as worse following such treatment, raises the possibility that certain tumour conditions could favour a less than desirable outcome. McMillan et al studied the effect of HBO on developing tumours in a hamster model and found two apparent effects of HBO.[31] They found fewer tumours in the group treated with HBO, but tumours that did develop were larger. They postulated two independent effects: inhibition of tumour growth during induction and enhancement of growth of pre-existing tumours. The inhibitory effects of HBO appear to predominate to some critical tumour bulk/size, at which point a tumour-enhancing effect may be observed. This is postulated to result from angioneogenesis.

In a very similar animal model Marx and Johnson also noted inhibition of tumourigenesis where tumour regression was noted with HBO alone.[32] Lindenschmidt et al observed the tumouricidal effect of HBO in lung tumours as possibly due to the interaction of cell membranes with free oxygen radicals such as peroxide and superoxide.[33] Where protective enzymes such as superoxide dismutase are in limited supply these radicals are demonstrated to destroy cell membranes with a mechanism similar to the action of some antineoplastics.[34]

Conclusions

IMPLICATIONS FOR CLINICAL PRACTICE

In the existing literature, the balance of evidence refutes the perception that HBO poses a risk for the patient with malignancy. Those patients for whom HBO is indicated for the treatment of LRTI should not have this therapy denied them because of the fear of increased tumour recurrence or metastatic spread. The level of evidence used in the synthesis of data produced results that differed between the reviews, in particular between no observed difference and improved outcome. The clinical conclusion, however, remained the same for all reviews. Despite the predominance of a predicted favourable outcome for patients with malignancy undergoing HBO, a better understanding is warranted to be able to identify minority groups with a measure of risk.

IMPLICATIONS FOR RESEARCH

A strong case has been made for large randomised trials of high methodological rigour to define the extent of benefit from the administration of HBO for patients with late radiation tissue injury.[19] By extending follow up on an existing trial the prerequisites of power to detect expected differences, suitable patients, consistency of dose and effective sham therapy will all ideally have been met. Elucidation of any adverse effects would need longer follow up, ideally to five years. Mortality data, quality-of-life scores and long-term cost utility could be gathered concurrently.

References

1 WHO. World Health Organization website: Cancer. <http://www.who.int/cancer/en/2005>

2 Anscher MS. The irreversibility of radiation induced fibrosis: Fact or folklore? *J Clin Oncol*. 2005; 23: 8551-2.

3 Marx RE. Radiation injury to tissue. In: Kindwall EP, Whelan HT, editors. *Hyperbaric medicine practice*. Flagstaff: Best Publishing; 1995. p. 665-718.

4 Feldmeier JJ, Heimbach RD, Davolt DA, Brakora MJ. Hyperbaric oxygen and the cancer patient: a survey of practice patterns. *Undersea Hyperb Med*. 1993; 20: 337-45.

5 Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissue: consequences and mechanisms. *Lancet Oncology*. 2003; 4: 529-36.

6 Johnson RJR, Lauchlan SC. Epidermoid carcinoma of the cervix treated by 60CO therapy and hyperbaric oxygen. In: *Proceedings of the third international congress on hyperbaric medicine*. 1966. p. 648-52.

7 Sachett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. *How to practice and teach evidence-based medicine*, 2nd edition. Edinburgh: Churchill Livingstone; 2000. p. 29-67.

8 Feldmeier J, Carl U, Hartmann K, Sminia P. Hyperbaric oxygen: Does it promote growth or recurrence of malignancy? *Undersea Hyperb Med*. 2003; 30: 1-18.

9 Oxford Centre for Evidence Based Medicine. *Levels of Evidence* (May 2001). <http://wwwcebm.net/levelsofevidence.asp>

10 Bennett MH, Feldmeier J, Smee R, Millross C. Hyperbaric oxygen for tumour sensitization to radiotherapy. In: *The Cochrane Database of Systematic Reviews*. 2005. 3.

11 Bennett MH, Feldmeier JJ, Smee R, Hampson N. Hyperbaric oxygen therapy for late radiation tissue injury. In: *The Cochrane Database of Systematic Reviews*. 2005. 3.

12 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality

associated with estimates of treatment effects in controlled trials. *JAMA*. 1995; 273: 408-12.
13 Bennett MH. *The evidence basis of diving and hyperbaric medicine – a synthesis of the high level clinical evidence with meta-analysis*. Australasia Digital Thesis Program. <http://adt.caul.edu.au/2006>
14 Oxford Centre for Evidence Based Medicine. *Critical Appraisal Worksheet for Harm /Aetiology*. 2001; <http://www.cebm.net/worksheet_harm.asp>
15 VandenBrenk HAS, Madigan JP, Kerr RC. An analysis of the progression and development of metastases in patients receiving x-radiation in hyperbaric oxygen. *Clin Radiol*. 1967; 18: 54-61.
16 Cade IS, McEwen JB. Megavoltage radiotherapy in hyperbaric oxygen. A controlled trial. *Cancer*. 1967; 20: 817-21.
17 Johnson RJR, Walton RJ. Sequential study of the effect of the addition of hyperbaric oxygen on the 5-year survival rates of carcinoma of the cervix treated with conventional radiation fractions. *Am J Roentgenol Ra*. 1974; 120: 111-7.
18 Henk JM, Kunkler PB, Smith CW. Radiotherapy and hyperbaric oxygen in head and neck cancer. Final report of first controlled clinical trial. *Lancet*. 1977; 8029: 101-3.
19 Henk JM, Smith CW. Radiotherapy and hyperbaric oxygen in head and neck cancer. Interim report of second clinical trial. *Lancet*. 1977; 8014: 104-8.
20 Bennet MB, Sealy R, Hockly J. The treatment of stage III squamous cell carcinoma of the cervix in air and in hyperbaric oxygen. In: *Proceedings 6th International congress on Hyperbaric Medicine*; 1977. p. 247-52.
21 Perrins DJD, Wiernik G. Controlled trials in carcinoma of the bladder. In: Smith G, editor. *Proceedings of the sixth international congress on hyperbaric medicine*. Abderdeen: University Press; 1977. p. 253-8.
22 Watson ER, Halnan KE, Dische S, Saunders MI, Cade IS, et al. Hyperbaric oxygen and radiotherapy: a medical research council trial in carcinoma of the cervix. *Br J Radiol*. 1978; 51: 879-87.
23 Dische S. Hyperbaric oxygen: the Medical Research Council trials and their clinical significance. *Br J Radiol*. 1979; 51: 888-94.
24 Brady LW, Plenk HP, Hanley JA, Glassburn JR, Kramer S, et al. Hyperbaric oxygen therapy for carcinoma of the cervix stages – IIB, IIA, IIIB and IVA: results of a randomized study by radiation therapy oncology group. *Int J Radiat Oncol Biol Phys*. 1981; 7: 991-8.
25 Eltorai I, Hart GB, Strauss MB, Khonsari R, Montroy RE. Does hyperbaric oxygen provoke an occult carcinoma in man? In: Kindwall EP, editor. *Proceedings of the eighth international congress on hyperbaric medicine*. San Pedro: Best Publishing; 1987. p. 18-29.
26 Denham W, Yeoh EK, Wittwer G, Ward CG, Ahmad AS, et al. Radiation therapy in hyperbaric oxygen for head and neck cancer at Royal Adelaide Hospital – 1964 to1969. *Int J Radiat Oncol Biol Phys*. 1987; 13: 201-8.
27 Xin PJ, Miao GC, Zong WC, Rong WC, Rong WS, et al. The influence of hyperbaric oxygenation on chemotherapy effects in patients with malignant lymphoma. In: Wen-ren Li, *Proceedings of the eleventh international congress on hyperbaric medicine*. Flagstaff: Best Publishing; 1993. p. 44-7.
28 Friedman GD. Introduction to epidemiology. In: *Primer of epidemiology*. New York: McGraw-Hill; 1994. p. 55-63.
29 Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965; 58: 295-300.
30 Bradfield JJ, Kinsella JB, Mader JT, Bridges EW, Calhoun KH. Rapid progression of head and neck squamous carcinoma after hyperbaric oxygenation. *Otolaryngol Head Neck Surg*. 1996; 114: 793-7.
31 McMillan T, Calhoun KH, Mader JT, Stiernberg CM, Rajaraman S. The effect of hyperbaric oxygen therapy on oral mucosal carcinoma. *Laryngoscope*. 1989; 99: 241-4.
32 Marx RE, Johnson RP. Problem wounds in oral and maxillofacial surgery: the role of hyperbaric oxygen. In: Davis JC, Hunt TK, editors. *Problem wounds: the role of oxygen*. New York: Elsevier; 1987. p. 107-9.
33 Lindenschmitt RC, Tryka AF, Witschi HP. Inhibition of mouse lung tumour development by hyperoxia. *Cancer Res*. 1986; 46: 1994-2000.
34 McCord JM, Fridovich I. The biology and pathology of oxygen radicals. *Ann Intern Med*. 1978; 89: 122-7.

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This paper is based on a dissertation for the degree of Master of Medical Science, The University of Auckland, and was presented by Dr Macdonald at the SPUMS ASM, New Zealand, 2007.
