Hyperbaric oxygenation for tumour sensitisation to radiotherapy

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A substantive amendment to this systematic review was last made on 16 July 2005. Cochrane reviews are regularly checked and updated if necessary.

Abstract

Background: Cancer is common and radiotherapy is one well-established treatment for some solid tumours. HBO may improve the ability of radiotherapy to kill hypoxic cancer cells, so the administration of radiotherapy while breathing HBO may result in a reduction in mortality and tumour recurrence.

Objective: To assess the benefits and harms of radiotherapy while breathing HBO.

Search strategy: In November 2004 we searched The Cochrane Central Register of Controlled Trials (CENTRAL), (The Cochrane Library Issue 3), MEDLINE, EMBASE , CINAHL, DORCTHIM and reference lists of articles. Relevant journals were handsearched.

Selection criteria: Randomised and quasi-randomised studies comparing the outcome of malignant tumours following radiation therapy while breathing HBO versus air (with or without sham therapy).

Data collection and analysis: Three reviewers independently evaluated the quality of the relevant trials using the method of Schulz (Schulz 1995) and extracted the data from the included trials.

Main results: Nineteen trials contributed to this review (2286 patients: 1103 allocated to HBO and 1153 control). With HBO, there was a reduction in mortality for head and neck cancers at both one year and five years after therapy (Relative risk (RR) 0.83, P = 0.03, number needed to treat (NNT) = 11 and RR 0.82, P = 0.03, NNT = 5 respectively), as well as improved local tumour control at three months (RR with HBOT 0.58, P = 0.006, NNT = 7). The effect of HBO varied with different fractionation schemes. Local tumour recurrence was less likely with HBO at one year (head and neck, RR 0.66, P < 0.0001, NNT = 5), two years (uterine cervix RR 0.60, P = 0.04, NNT = 5) and five years (head and neck (RR 0.77, P = 0.01). Any advantage is achieved at the cost of some adverse effects. There was a significant increase in the rate of both severe radiation tissue injury (RR 2.35, P < 0.0001, (number needed to harm (NNH) = 8) and the chance of seizures during therapy (RR 6.76, P = 0.03, NNH 22) with HBO.

Reviewers' conclusions: There is some evidence that HBO improves local tumour control and mortality for cancers of the head and neck, and local tumour recurrence in cancers of the head and neck, and uterine cervix. These benefits may only occur with unusual fractionation schemes. HBO is associated with significant adverse effects including oxygen toxic seizures and severe tissue radiation injury. The methodological and reporting inadequacies of the primary studies included in this review demand a cautious interpretation. More research is needed for head and neck cancer, but is probably not justified for bladder cancer. There is little evidence available concerning malignancies at other anatomical sites on which to base a recommendation.

Background

Invasive cancer continues to be a major world health problem. According to World Health Organization (WHO) statistics, more than 10 million people are diagnosed with cancer every year, and it is estimated there will be 15 million new cases every year by 2020. Cancer causes 6 million deaths every year or 12% of deaths worldwide (WHO 2004), and being associated with approximately 0.5 million deaths each year is the second leading cause of death in the USA (ACS 2004; Hotes 2003). Radiotherapy is a well-established treatment of suitable malignancies in a wide variety of anatomical areas. In the USA, approximately 1.2 million new cases are diagnosed annually, and about 50% of these will be treated with radiation (Jemal 2002).

Many, if not all, solid tumours include regions where there is significant hypoxia and it has been established for some years that these areas of hypoxia are resistant to therapy (Gray 1953; Overgaard 1996). A body of evidence exists to suggest that this radio-resistance can be overcome by a variety of measures including increasing oxygen pressure within the tumour (e.g. high oxygen content breathing, administration of red blood cells), and administration of radiation sensitising agents (e.g. nitroimidazoles such as nimorazole) (Bush 1986; Grau 1992; Overgaard 1994; Rubin 1979). The effectiveness of such measures remains controversial, and despite more than 10,000 patients in total being randomized to a variety of treatment and control groups, no clinically important benefits of these treatments have been conclusively demonstrated. One review with meta-analysis suggested a reduction in tumour recurrence at the site irradiated and in the lymph nodes draining that site when all methods to modify tumour hypoxia were combined and compared to control, with an odds ratio of 0.83 (95% confidence interval (CI) 0.77 to 0.89) (Overgaard 1996). The search strategy, inclusion/exclusion criteria for trials, definition of outcomes and statistical methods of this review were not clear from that report.

One attractive method for increasing oxygen pressure in hypoxic areas is the administration of 100% oxygen at greater than one atmosphere total pressure, a procedure known as hyperbaric oxygenation (HBO). HBO was first used for this purpose in the 1960s and reported by Churchill-Davidson (Churchill 1968). The technique of administering radiation whilst confined in a hyperbaric chamber was adopted in a number of centres around the world, but inherent difficulties with the physical requirements and the advent of orally administered agents to improve tumour sensitivity to radiation led to the abandonment of this combined approach during the 1980s. These decisions were made despite the publication of a number of promising clinical trials with HBO, and it has been suggested HBO was abandoned before a measured evaluation was made of the true clinical impact (Overgaard 1996). While many of the trials using HBO were included in this review by Overgaard, we believe a structured systematic search may reveal further evidence, and are aware of at least two randomised trials published after 1996 (Dische 1999; Haffty 1999).

HBO remains relatively widely available in North America (where there are more than 300 facilities registered with the Undersea and Hyperbaric Medical Society [UHMS]), Russia, China and Cuba, but is less well-established in Europe and Australasia (UHMS 2001). Treatment involves placing the patient in a compression chamber, increasing the environmental pressure within the chamber, and administering 100% oxygen for respiration. In this way, it is possible to deliver a greatly increased pressure of oxygen to the tissues. Typically, treatments for tumour oxygen sensitisation involve pressurisation to between 2.0 and 4.0 atmospheres absolute (ATA) for periods between 20 and 30 minutes for pre-oxygenation, following which the radiation therapy is delivered while the patient continues to breathe oxygen at pressure. A range of radiation fractionation and dosing schemes has been suggested.

HBO is associated with some risk of adverse effects including damage to the ears, sinuses and lungs from the effects of pressure, temporary worsening of myopia, claustrophobia and oxygen poisoning. Although serious adverse events are rare, HBO cannot be regarded as an entirely benign intervention. It has further been suggested that HBOT may increase the incidence

and/or rate of growth of local recurrence or remote metastatic disease in patients with a history of malignancy, although a recent comprehensive review fails to support these concerns (Feldmeier 2003).

Objectives

The aim of this review was to assess the evidence for the benefit of simultaneously combining radiation therapy and HBO for the treatment of solid tumours.

(1) Does the addition of HBO to radiation therapy:

- Reduce mortality at any time following therapy?
- Increase local tumour response?
- Reduce the incidence of local recurrence?
- Reduce the incidence of metastatic spread?
- Improve the quality of life for these patients?

(2) Does sensitisation to radiation therapy with HBO, compared to other agents, produce any of the benefits above?

(3) Is HBO administration safe in this setting?

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomized controlled trials that:

- compared the effect of simultaneous HBO and radiation therapy to regimens employing radiation therapy while breathing air, or
- compared the effect of simultaneous HBO and radiation therapy to regimens employing another sensitising therapy and radiation therapy.

Types of participants

Patients with solid tumours of whatever part where radiation therapy is indicated. No restrictions were made on the basis of age or gender.

Types of intervention

We included studies that compared treatment regimens which include HBO with similar regimens that exclude HBO, with or without the use of other sensitisers. Where co-interventions or fractionation regimens differed significantly between studies this was clearly stated and the implications discussed, or appropriate subgroup analysis performed.

HBO administered in a compression chamber at any pressure above 1.0 ATA, either simultaneously with or immediately following radiation therapy, were accepted.

Types of outcome measures

Studies were eligible for inclusion if they reported any of the following outcome measures:

- Primary outcomes:

- (1) Mortality rate at any time
- (2) Complete or partial failure to control local tumour at any time
- (3) Local recurrence rate at any time
- (4) Metastatic disease at any time.

- Secondary outcomes:
- (5) Quality of life (QOL) assessment.

- Adverse effects of HBO
- Specific to combined HBO/radiation therapy:
- (6) Acute tissue reaction in irradiated area
- (7) Late tissue injury in irradiated area
- (8) Pain scores.

- General relating to HBO:
- (9) Visual disturbance (short and long-term)
- (10) Barotrauma (aural, sinus, pulmonary in the short and long-term)
- (11) Oxygen toxicity (short-term).

Any other recorded adverse effects would be reported and discussed.

Search strategy for identification of studies

See: Cochrane Gynaecological Cancer Group search strategy

It was our intention to capture both published and unpublished studies.

- Electronic searches
- We searched the following (from inception) in November 2004:
- CENTRAL on the Cochrane Library (CENTRAL Issue 3, 2004), MEDLINE (Ovid), CINAHL, EMBASE and an additional database developed in our hyperbaric facility (the Database of Randomized Trials in Hyperbaric Medicine, Bennett 2004). The search strategy was broad and the keywords in the following strategies were adapted as appropriate. The EMBASE and MEDLINE (OVID) strategies are given in Table 01.

In addition we made a systematic search for relevant controlled trials in specific hyperbaric literature sources as follows.

- Experts in the field and leading hyperbaric therapy centres (as identified by personal communication and searching the Internet) were contacted and asked for additional relevant data in terms of published or unpublished randomized trials.
- Handsearch of relevant hyperbaric textbooks (Kindwall, Jain, Marroni, Bakker, Bennett and Elliot), journals (Undersea and Hyperbaric Medicine, Hyperbaric Medicine Review, South Pacific Underwater Medicine Society (SPUMS) Journal, European Journal of Hyperbaric Medicine and Aviation, Space and Environmental Medicine Journal) and conference proceedings (Undersea and Hyperbaric Medical Society, SPUMS, European Undersea and Baromedical Society, International Congress of Hyperbaric Medicine) published since 1980.
- Contact authors of relevant studies to request details of unpublished or ongoing investigations.
- Examine the reference list of all trials for inclusion in this review.

All languages were considered. Authors were contacted if there was any ambiguity about the published data.

Methods of the review

- Trial identification
- Records retrieved by the initial search were scanned by two reviewers (MB and RS) to identify trials that meet the inclusion criteria. Full-text articles were retrieved and reviewed by the same two reviewers for the purpose of applying inclusion criteria independently. In all instances, differences of opinion were to be resolved by discussion among the reviewers and referral to a third reviewer (CM) for a decision. This was not necessary, however.

- Data extraction
- Data from the studies was extracted independently by two authors using standardized forms. Abstracted data included the following characteristics: methods (number eligible and randomised, adequacy of randomisation, allocation concealment, blinding, completeness of follow-up); participant characteristics and exclusions; interventions; outcomes (dichotomous variables [number with outcome of interest]; continuous variables [mean and standard deviation]). We attempted to contact primary authors when missing data was encountered or if necessary data are not clearly stated. All differences were resolved by discussion among the reviewers.

- Quality assessment
- Study quality was assessed using an adaptation of the method outlined in Schulz 1995 (Schulz 1995). Results from the study quality are presented in a descriptive manner. The following characteristics were assessed:

- Adequacy of the randomization process:
- A - Adequate sequence generation is reported using random number tables, computer random number generator, coin tossing, or shuffling
- B - Did not specify one of the adequate reported methods in (A) but mentioned randomization method
- C - Other methods of allocation that appear to be unbiased.

- Adequacy of the allocation concealment process:
- A - Adequate measures to conceal allocations such as central randomization; serially numbered, opaque, sealed envelopes; or other description that contained convincing elements of concealment
- B- Unclearly concealed trials in which the author either did not report an allocation concealment approach at all, or reported an approach that did not fall into one of the categories in (A)
- C- Inadequately concealed trials in which method of allocation is not concealed such as alternation methods or use of case record numbers.

- Potential for selection bias after allocation:
- A- Trials where an intention to treat analysis is possible and few losses to follow-up are noted
- B- Trials which reported exclusions (as listed in A but exclusions were less than 10%)
- C- No reporting on exclusions or exclusions greater than 10% or wide differences in exclusions between groups.

- Level of masking (Treatment provider, patient, outcome assessor):
- A- Double or triple blind
- B- Single blind
- C- Non-blind.

- Analyses

- We used a fixed-effect model where there was no evidence of significant heterogeneity between studies and a random effects model when such heterogeneity is likely (DerSimonian 1986). Consideration was given to the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. Heterogeneity was tested using the I2 statistic and significant heterogeneity assumed if I2 was greater than 40% (more than 40% of the variability in outcome between trials could not be explained by sampling variation) (Higgins 2003). Where appropriate data were available or could be extracted, we intended to compare survival over time using the log Hazard Ratio and variance (Parmar 1998). For proportions (dichotomous outcomes), RR was used. Continuous data would have been converted to the weighted mean difference (WMD) using the inverse variance method and an overall WMD calculated. Selection bias was tested using funnel plot, depending on the number of clinical trials included in the individual outcomes.

We considered sensitivity analysis on the basis of the presence or absence of clear allocation concealment, however this was not appropriate.

- Where appropriate data existed, we performed subgroup analysis based on:
- (1) Age - adults versus children (less than 16 years)
- (2) Dose of oxygen received (pressure less than 2.5 ATA versus greater than or equal to 2.5 ATA)
- (3) Dose and fractionation of radiation therapy (large fractions [total dose over 12 or fewer fractions] versus conventional fractions [total does over >12 fractions])
- (4) Simultaneous versus sequential administration of HBOT.

Description of studies

We identified 103 publications apparently dealing with the use of HBO in conjunction with therapeutic radiotherapy. Initial examination of abstracts where available confirmed 18 were case reports or case series, 14 were reviews without new data, 13 were not clinical studies, 13 were dealing with conditions other than tumours, three were non-random comparative studies and one was a letter. These reports were excluded, leaving 41 possible comparative trials. After appraisal of the full reports we further excluded three as reviews without new data and 19 as abstracts or interim reports of randomised controlled trials (RCTs) where the data was reported more fully in another publication (see table 'Characteristics of excluded studies'). The other 19 trials were accepted into the review.

The included trials were published between 1967 and 1999, and the reviewers are unaware of any on-going RCTs in the area. They report data concerning the treatment of malignant tumours from several different sites: head and neck (Berry 1979; Chang 1973; Haffty 1999; Henk 1977a; Henk 1986; Sause 1979; Sealy 1986; Shigematsu 1973; Tobin 1971; Van Den Brenk 1968) ,uterine cervix (Brady 1981; Dische 1999; Fletcher 1977; Glassburn 1974; Tobin 1971; Ward 1979; Watson 1978), urinary bladder (Cade 1967; Cade 1978; Plenk 1972; Tobin 1971; Van Den Brenk 1968), bronchus (Cade 1967), rectum (Tobin 1971), brain (Tobin 1971) and oesophagus (Tobin 1971). In total, these trials enrolled 2286 subjects, of which 1103 were allocated to receive HBO and 1153 to control (no allocation information was available on 30 subjects). The largest (Dische 1999) accounts for 14.7% of cases in this review and the smallest (Berry 1979) for 1%. (See table: 'Characteristics of included studies').

The dose of oxygen per treatment session in the HBO arm was remarkably uniform, with all trials except one administering external beam radiation therapy while at 3 ATA for between 30 and 40 minutes. The exception was Haffty 1999 who used oxygen at four ATA and required all patients to be anaesthetised and intubated because of the risk of oxygen toxic seizures. The total number of treatment sessions varied widely however. The shortest fractionation scheme was two sessions only, separated by three weeks (Haffty 1999) and the longest was 40 sessions over eight weeks (Cade 1978; Cade 1967). External beam radiation dose also varied widely in both arms of the studies with a range from 2600 rads (Haffty 1999) to 7000 rads (Shigematsu 1973) for the control groups and from 2300 rads (Haffty 1999) to 6000 rads (Cade

1967; Cade 1978) for the HBO groups. Most studies of the treatment of uterine cervical cancer also included intra-cavitary placement of radioactive material, the exception being Tobin 1971. One trial examined the efficacy of HBO plus a second sensitising agent misonidazole (Sealy 1986).

None of the included studies employed a sham therapy, so no comparisons between the efficacy of HBO and air breathing during radiotherapy were blinded to either patients or treatment providers.The follow-up period varied between trials, ranging from six months (Van Den Brenk 1968) to 10 years (Haffty 1999), although most studies followed subjects for between two and five years. All included studies reported at least one outcome of interest. Of the outcomes identified above, these trials reported data on all four primary outcomes, and on adverse effects of therapy, but not the secondary outcome of quality of life.

Other outcomes (including non-clinical) reported include: selected cause mortality (Henk 1977a), development of radiation tissue effects (Henk 1977a; Shigematsu 1973), disease-free survival (Fletcher 1977), survival according to histology (Cade 1978), development of new primary malignancy (Sealy 1986), relationship between dose and morbidity (Brady 1981; Dische 1999) and the incidence of salvage surgery (Henk 1986; Sause 1979).

Methodological quality

Details of the quality assessment are given in the table 'Characteristics of included studies'. In general, study quality was assessed as fair with regard to methodology. The significance of variations in quality detailed below is unclear and given that relatively few analyses could be pooled, study quality was not used as a basis for sensitivity analysis.

- Randomisation
- Randomisation procedures were described as by centrally supplied sealed envelopes in Berry 1979; Cade 1967; Cade 1978; Dische 1999; Henk 1986; Ward 1979 and Watson 1978. Although not stated in the report, it is likely this is true also of Henk 1977a, as this trial was undertaken under the auspices of the same group (British Medical Council). Three trials (Chang 1973; Haffty 1999; Sealy 1986) also employed a sealed envelope system, while Plenk 1972 used a random number table and Tobin 1971 a card drawn by a disinterested person. The method of randomisation was not stated in four studies (Brady 1981; Fletcher 1977; Glassburn 1974; Sause 1979) and quasi-random in two studies: Shigematsu 1973 implies a method based on the registration number, while Van Den Brenk 1968 used birth date.

- Concealment of allocation
- Allocation concealment appeared adequate for the British Medical Council trials but in none of the remaining studies is there a clear indication that the investigators were unable to predict the prospective group to which a participant would be allocated.

- Subject baseline characteristics
- Subjects entered into all trials had proven malignancies where radiotherapy was the treatment of choice in the anatomical area of interest to the particular trial. Many trials included only subjects who were less than 75 years old. Details of staging are given in the table 'Characterisitics of included studies', but were generally reasonably consistent across trials.

- Blinding
- None of the studies included were blinded in any way.

- Intention-to-treat analysis
- Nine studies reported no losses to follow-up (Berry 1979; Cade 1967; Chang 1973; Fletcher 1977; Glassburn 1974; Haffty 1999; Shigematsu 1973; Van Den Brenk 1968; Watson 1978). Two studies reported analysing patients randomised to receive HBO in

the control group (Berry 1979; Ward 1979), while 10 studies reported losses to follow-up, none of which appear in analysis in those reports. The highest proportion of lost subjects was in Plenk 1972, who lost 22 subjects at final follow-up, 55% of the total enrolled. Sensitivity analysis using best and worse case scenarios have been performed where possible for dichotomous outcomes involving those studies with losses to follow-up.

None of the included studies specifically indicated an intention to treat approach, however 8 of 19 studies (see above) reported full follow-up and did not report any protocol violation.

Results

Primary outcomes

- 1. Death rate
- All trials reported mortality rate at some time, and therefore contribute to this outcome. There was insufficient data in any trial to permit calculation of survival over time using the log Hazard Ratio.

- One year mortality
- 1.1 Mortality at one year with head and neck cancer (comparison 1, outcomes 01, 02, 03)
- Nine trials reported this outcome (Berry 1979; Chang 1973; Haffty 1999; Henk 1977a; Henk 1986; Sealy 1986; Shigematsu 1973; Tobin 1971; Van Den Brenk 1968), reporting on 710 subjects after exclusion of withdrawals (31% of the total subjects in this review), with 339 (48%) allocated to HBOT and 371 (52%) to control. Over all fractionation schemes there was a statistically significant reduction in the proportion of subjects dying within one year after receiving radiation therapy with HBO (the RR of death with HBO was 0.83, 95% CI 0.70 to 0.98, P = 0.03). There was no evidence of substantial heterogeneity between trials overall (I2 = 0%), but some heterogeneity for the trials using fewer than 12 sessions in HBO compared to more than 12 in air (I2 =39%), so these results are achieved using a random effects model. There is an absolute risk reduction of 9.2% when using HBOT (NNT to avoid one death 11, 95% CI 7 to 52).

The reduction in risk of death overall is sensitive to the allocation of withdrawals (best case scenario RR 0.73, 95% CI 0.62 to 0.85, P = 0.0001; worst case RR 0.93, 95% CI 0.76 to 1.15, P = 0.51), however, the risk in those receiving 12 fractions with HBO versus more than 12 fractions in air is not sensitive to allocation of withdrawals (worst case RR 0.72, 95% CI 0.56 to 0.92, P = 0.01).

- 1.2 Mortality at one year with cancer of the uterine cervix (comparison 1, outcomes 04, 05, 06)
- Four trials reported this outcome (Dische 1999; Tobin 1971; Ward 1979; Watson 1978) reporting on 751 subjects after exclusion of withdrawals (33% of the total subjects in this review), with 348 (46%) allocated to HBOT and 384 (54%) to control. There was no statistically significant reduction in the proportion of subjects dying within one year after receiving radiation therapy with HBO (RR 0.88, 95% CI 0.69 to 1.11, P = 0.27), neither did subgroup analysis suggest any benefit with different fractionation schemes. There was no evidence of substantial heterogeneity between trials overall (I2 = 0%) and this result is achieved using a fixed effects model. The risk of death was not sensitive to the allocation of withdrawals (best case scenario RR 0.87, 95%CI 0.69 to 1.10, P = 0.25; worst case RR 0.91, 95% CI 0.72 to 1.15, P = 0.43).

- 1.3 Mortality at one year with cancer of the urinary bladder (comparison 1, outcomes 07, 08, 09)

- Four trials reported this outcome (Cade 1967; Cade 1978; Plenk 1972; Van Den Brenk 1968) reporting on 330 subjects after exclusion of withdrawals (14% of the total subjects in this review), with 165 allocated to both HBO and control. There was no statistically significant reduction in the proportion of subjects dying within one year after receiving radiation therapy with HBO (RR 0.97, 95% CI 0.74 to 1.27, P =0 .82), neither did subgroup analysis suggest any benefit with different fractionation schemes. There was moderate heterogeneity between trials overall (I2 = 39%) and this result is achieved using a fixed effects model. The risk of death was not sensitive to the allocation of withdrawals (best case scenario RR 0.92, 95% CI 0.71 to 1.21, P = 0.56; worst case RR 1.03, 95% CI 0.78 to 1.34, P = 0.86).

- 1.4 Mortality at one year with carcinoma of the bronchus (comparison 1, outcome 10)
- One trial reported this outcome (Cade 1967) reporting on 49 subjects after exclusion of withdrawals (2% of the total subjects in this review), with 25 (51%) allocated to HBO and 24 (49%) to control. There was no statistically significant difference in the proportion of subjects dying within one year after receiving radiation therapy with HBO (RR 1.09, 95% CI 0.72 to 1.64, P = 0.69).

- 1.5 Mortality at one year with carcinoma of the rectum (comparison 1, outcome 11)
- One trial reported this outcome (Tobin 1971) involving four subjects (0.2% of the total subjects in this review), with 2 allocated to both HBO and control. Both subjects died following HBO and one of those receiving control. There was no statistically significant difference in the proportion of subjects dying within one year after receiving radiation therapy with HBO (RR 5.0, 95% CI 0.11 to 220.62, P = 0.4).

- 1.6 Mortality at one year with carcinoma of the oesophagus (comparison 1, outcome 12)
- One trial reported this outcome (Tobin 1971) involving four subjects (0.2% of the total subjects in this review), with 2 allocated to both HBO and control. One subject died following HBO and both of those receiving control. There was no statistically significant difference in the proportion of subjects dying within one year after receiving radiation therapy with HBO (RR 0.2, 95% CI 0.00 to 8.82, P = 0.4).

- 1.7 Mortality at one year with glioblastoma (comparison 1, outcome 13)
- One trial reported this outcome (Tobin 1971) involving four subjects (0.2% of the total subjects in this review), with 2 allocated to both HBO and control. All subjects died within one year, making analysis unhelpful.

- Mortality at two years:
- 1.8 Mortality at two years with head and neck cancer (comparison 2, outcomes 01, 02, 03)
- Three trials reported this outcome (Haffty 1999; Sealy 1986; Tobin 1971), reporting on 189 subjects after exclusion of withdrawals (8% of the total subjects in this review), with 92 (49%) allocated to HBO and 97 (51%) to control. Sealy 1986 contributes 65% of the weight to this analysis. There was no statistically significant reduction in the proportion of subjects dying within two years after receiving radiation therapy with HBO (RR 0.84, 95% CI 0.41 to 1.73, P = 0.64), neither did subgroup analysis suggest any benefit with different fractionation schemes. There was no evidence of substantial heterogeneity between trials overall (I2 = 0%) and this result is achieved using a fixed effects model. The reduction in risk of death is not sensitive to the allocation of withdrawals (best case scenario RR 0.92, 95% CI 0.79 to 1.07, P = 0.28; worst case RR 1.00, 95% CI 0.86 to 1.15, P = 0.97).

- 1.9 Mortality at two years with cancer of the uterine cervix (comparison 2, outcome 04)
- Four trials reported this outcome (Fletcher 1977; Glassburn 1974; Tobin 1971; Watson 1978), reporting on 607 subjects after exclusion of withdrawals (27% of the total subjects in this review), with 294 (48%) allocated to HBO and 313 (52%) to control. There was no statistically significant reduction in the proportion of subjects dying within two years after receiving radiation therapy with HBO (RR 0.94, 95% CI 0.76 to 1.15, P =

0.53), neither did subgroup analysis suggest any benefit with different fractionation schemes. There was evidence of moderate heterogeneity between trials overall (I2 =36%) and this result is achieved using a random effects model. No trials had suffered any losses to follow-up after randomisation.

- 1.10 Mortality at two years with urinary bladder carcinoma (comparison 2, outcomes 05, 06, 07)
- Two trials reported this outcome (Plenk 1972; Tobin 1971), reporting on 24 subjects after exclusion of withdrawals (1% of the total subjects in this review), with 12 allocated to both HBO and control.Plenk 1972 contributes 71% of the weight to this analysis. There was no statistically significant difference in the proportion of subjects dying within two years after receiving radiation therapy with HBO (RR 2.83, 95% CI 0.35 to 23.09, P = 0.33). There was no evidence of substantial heterogeneity between trials overall (I2 = 0%) and this result is achieved using a fixed effects model. The risk of death with HBO is sensitive to the allocation of the large number of losses to follow-up in the Plenk 1972 trial (best case scenario RR 0.47, 95% CI 0.04 to 5.24, P = 0.54; worst case RR 5.7, 95% CI 2.26 to 14.37, P = 0.0002).

- Mortality at five years:
- 1.11 Mortality at five years with head and neck cancer (comparison 3, outcomes 01, 02, 03)
- Six trials reported this outcome (Berry 1979; Chang 1973; Haffty 1999; Henk 1977a; Henk 1986; Sause 1979), reporting on 550 subjects after exclusion of withdrawals (24% of the total subjects in this review), with 258 (47%) allocated to HBO and 292 (53%) to control. Over all fractionation schemes there was a statistically significant reduction in the proportion of subjects dying within five years after receiving radiation therapy with HBO (RR 0.82, 95% CI 0.69 to 0.98, P = 0.03), however subgroup analysis by fractionation scheme suggests the benefit may be restricted to those who receive 12 or fewer fractions when compared to those who receive a standard fractionation scheme of more than 12 sessions (RR in this group 0.69, 95%CI 0.53 to 0.89, P = 0.004; RR for 12 or fewer fractions in each group 0.96, 95% CI 0.75 to 1.22, P = 0.73). There was moderate heterogeneity between trials overall (I2 = 37%), however little evidence for heterogeneity within each subgroup of fraction schemes, and this result is achieved using a fixed effects model. There is an absolute risk reduction of 7.5% (NNT 14, 95% CI 7 to infinity) overall, but a 20.9% reduction for those who receive 12 or fewer fractions when compared to those who receive a standard fractionation scheme of more than 12 sessions (NNT 5, 95% CI 3 to 14).

The overall reduction in risk of death is sensitive to the allocation of withdrawals (best case scenario RR 0.77, 95% CI 0.64 to 0.92, P = 0.004; worst case RR 0.96, 95% CI 0.81 to 1.13, P = 0.6), however, the risk in those receiving 12 fractions with HBO versus more than 12 fractions in air is not sensisitive to allocation of withdrawals (worst case RR 0.75, 95% CI 0.59 to 0.96, P = 0.02).

- 1.12 Mortality at five years with cancer of the uterine cervix (comparison 3, outcomes 04, 05, 06)
- Four trials reported this outcome (Brady 1981; Dische 1999; Ward 1979; Watson 1978), reporting on 772 subjects after exclusion of withdrawals (34% of the total subjects in this review), with 367 (48%) allocated to HBO and 405 (52%) to control. There was no significant reduction in the proportion of subjects dying within five years after receiving radiation therapy with HBO (RR 0.95, 95% CI 0.80 to 1.14, P = 0.59). There was considerable heterogeneity between trials (I2 = 63%) for which Watson 1978 is largely responsible (suggesting a strong beneficial effect of HBO). This result is therefore the result of a random effects model. The result was not sensitive to the allocation of withdrawals (best case scenario RR 0.92, 95% CI 0.77 to 1.09, P = 0.32; worst case RR 0.98, 95% CI 0.81 to 1.18, P = 0.8).

- 1.13 Mortality at five years with urinary bladder cancer (comparison 3, outcome 07)

- One trial reported this outcome (Cade 1978), reporting on 236 subjects after exclusion of withdrawals (10% of the total subjects in this review), with 118 allocated to each of HBO and control. There was no reduction in the proportion of subjects dying within five years after receiving radiation therapy with HBO (RR 1.13, 95% CI 0.65 to 1.98, P = 0.67). Sensitivity analysis for the five subjects lost to analysis could not be performed due to lack of information about original allocation.

2. Failure to control local tumour

- 2.1 Failure to control local tumour at three months in head and neck cancer (comparison 4, outcome 01)
- Four trials reported this outcome (Haffty 1999; Henk 1977a; Shigematsu 1973; Van Den Brenk 1968), reporting on 446 subjects after exclusion of withdrawals (20% of the total subjects in this review), with 212 (48%) allocated to HBO and 234 (52%) to control. Over all fractionation schemes there was a statistically significant improvement in the chance of local tumour control at three months following radiation therapy with HBO (RR of failure with HBO 0.58, 95% CI 0.39 to 0.85, P = 0.006). Subgroup analysis by fractionation scheme suggests the magnitude of benefit remains similar, but statistical significance is restricted to a comparison between those who receive 12 or fewer fractions in both groups (RR in this group 0.54, 95% CI 0.34 to 0.88, P = 0.01; RR for 12 or fewer fractions in HBOT versus more than 12 with control 0.67, 95% CI 0.24 to 1.82, P = 0.43). There was moderate heterogeneity between trials overall (I2 = 26%), and this result is achieved using a fixed effects model. There is an absolute risk reduction of 15% when using HBOT (NNT to avoid one failure to control 7, 95% CI 5 to 17). The overall reduction in failure to control tumour is marginally sensitive to the allocation of withdrawals (best case scenario RR 0.57, 95% CI 0.41 to 0.78, P = 0.0005; worst case RR 0.59, 95% CI 0.35 to 1.00, P = 0.05).

3. Local recurrence

- Local recurrence at one year
- 3.1 Local recurrence at one year with head and neck cancer (comparison 5, outcomes 01, 02, 03)
- Five trials reported this outcome (Haffty 1999; Henk 1977a; Henk 1986; Sealy 1986; Shigematsu 1973), reporting on 714 subjects after exclusion of withdrawals (31% of the total subjects in this review), with 338 (47%) allocated to HBO and 376 (53%) to control. Over all fractionation schemes there was a statistically significant reduction in the incidence of local tumour recurrence following radiation therapy with HBO (RR 0.66, 95% CI 0.56 to 0.78, P < 0.00001). Subgroup analysis by fractionation scheme suggests the benefit is independent of fractionation scheme (RR with fewer than 12 fractions in each group 0.62, 95% CI 0.50 to 0.77, P < 0.0001; RR for 12 or fewer fractions in HBO versus more than 12 with control 0.73, 95% CI 0.56 to 0.80, P = 0.01). There was no evidence of heterogeneity between trials overall (I2 = 0%) and this result is achieved using a fixed effects model. There is an absolute risk reduction of 21.1% when using HBOT (NNT to avoid one recurrence 5, 95% CI 4 to 8). The overall reduction in failure to control tumour is not sensitive to the allocation of withdrawals (best case scenario RR 0.61, 95% CI 0.51 to 0.71, P < 0.00001; worst case RR 0.75, 95% CI 0.65 to 0.87, P = 0.0002).

- 3.2 Local recurrence at one year with cancer of the uterine cervix (comparison 5, outcomes 04, 05, 06)
- Three trials reported this outcome (Dische 1999; Ward 1979; Watson 1978), reporting on 714 subjects after exclusion of withdrawals (31% of the total subjects in this review), with 338 (47%) allocated to HBO and 376 (53%) to control. Over all fractionation schemes there was no statistically significant reduction in the incidence of local tumour recurrence following radiation therapy with HBO (RR 0.82, 95% CI 0.63 to 1.06, P = 0.13), with little difference between subgroups with different fractionation schemes. There was evidence of moderate heterogeneity between trials overall (I2 = 23%), but significant heterogeneity when comparing groups who had received fewer than 12

fractions (I2 = 37%), and this result is achieved using a random effects model. The risk of recurrence was not sensitive to the allocation of those lost to follow-up (best case scenario RR 0.81, 95% CI 0.63 to 1.02, P = 0.08; worst case RR 0.87, 95% CI 0.63 to 1.19, P = 0.38).

- Local recurrence at two years
- 3.3 Local recurrence at two years with head and neck cancer (comparison 6 outcome 01)
- One trial reported this outcome (Haffty 1999), involving 48 subjects (2% of the total subjects in this review), with 23 (48%) allocated to HBO and 25 (52%) to control. There was no significant reduction in the incidence of local tumour recurrence following radiation therapy with HBO (RR 0.83, 95% CI 0.60 to 1.14, P = 0.25).

- 3.4 Local recurrence at two years with cancer of the uterine cervix (comparison 6, outcome 02)
- Two trials reported this outcome (Glassburn 1974; Watson 1978), reporting on 360 subjects after exclusion of withdrawals (16% of the total subjects in this review), with 178 (49%) allocated to HBO and 182 (51%) to control. Watson 1978 contributes 73% of the weight to this analysis. Over all fractionation schemes there was a statistically significant reduction in the incidence of local tumour recurrence following radiation therapy with HBO (RR 0.60, 95% CI 0.38 to 0.97, P = 0.04), however subgroup analysis by fractionation scheme suggests the benefit may be restricted to those who receive 12 or fewer fractions in each group (RR in this group 0.53, 95% CI 0.37 to 0.77, P = 0.0007; RR for more than 12 fractions in each group 0.68, 95% CI 0.26 to 1.73, P = 0.41).There was evidence of significant heterogeneity between trials overall (I2 =67%) and this result is achieved using a random effects model. Overall, there is a risk reduction of 23% when using HBO (NNT to avoid one recurrence 5, 95% CI 4 to 8), while the reduction for the comparison between groups receiving fewer than 12 fractions was 41.3%, (NNT 3, 95% CI 2 to 5). There were no losses to follow-up for any of these studies.

- Local recurrence at five years
- 3.5 Local recurrence at five years with head and neck cancer (comparison 7, outcomes 01, 02, 03)
- Five trials reported this outcome (Berry 1979; Haffty 1999; Henk 1977a; Henk 1986; Sause 1979), reporting on 495 subjects after exclusion of withdrawals (22% of the total subjects in this review), with 229 (46%) allocated to HBO and 266 (54%) to control. Over all fractionation schemes there was a statistically significant reduction in the incidence of local tumour recurrence following radiation therapy with HBO (RR 0.77, 95% CI 0.62 to 0.95, P = 0.01). Subgroup analysis by fractionation scheme suggests the benefit may be restricted to those trials comparing fewer than 12 fractions in each group (RR with fewer than 12 fractions in each group 0.74, 95%CI 0.62 to 0.88, P = 0.0009; RR for 12 or fewer fractions in HBOT versus more than 12 with control 0.75, 95% CI 0.39 to 1.43, P = 0.38). There was evidence of moderate heterogeneity between trials overall (I2 =32%), and substantial heterogeneity for those trials comparing fewer than 12 fractions in HBO with 12 or more fractions in control (I2 = 63%), and this result is achieved using a random effects model. Overall, there is an absolute risk reduction (ARR) of 19% when using HBO (NNT to avoid one recurrence 6, 95% CI 4 to 11), and the ARR is also 19% for trials comparing fewer than 12 fractions in each group, (NNT 6, 95% CI 4 to 12).
- The overall reduction in failure to control tumour is sensitive to the allocation of withdrawals (best case scenario RR 0.70, 95% CI 0.57 to 0.86, P = 0.0008; worst case RR 0.84, 95% CI 0.66 to 1.06, P = 0.14).

- 3.6 Local recurrence at five years with cancer of the uterine cervix (comparison 7, outcomes 04, 05, 06)
- Four trials reported this outcome (Brady 1981; Dische 1999; Ward 1979; Watson 1978), involving 772 subjects (34% of the total subjects in this review), with 367 (48%) allocated to HBO and 405 (52%) to control. There was no significant reduction in the

incidence of local tumour recurrence following radiation therapy with HBOT (RR 0.85, 95% CI 0.65 to 1.13, P = 0.27). Subgroup analysis did not suggest benefit with any particular fractionation scheme. There was evidence of significant heterogeneity between trials overall (I2 = 68%) and this result is achieved using a random effects model. The analysis is sensitive to the allocation of withdrawals (best case scenario RR 0.83, 95% CI 0.72 to 0.97, P = 0.02; worst case RR 0.89, 95%CI 0.77 to 1.03, P = 0.11).

4. Development of metastasis

- Metastases at one year
- 4.1 Metastases at one year with cancer of the uterine cervix (comparison 8, outcome 01)
- One trial reported this outcome (Watson 1978), involving 320 subjects (23% of the total subjects in this review, with 161 (50.3%) allocated to HBO and 159 (49.7%) to control. There were no withdrawals or losses to folow-up. There was no significant reduction in the incidence of metastases following radiation therapy with HBO (RR 0.79, 95% CI 0.52 to 1.19, P = 0.26). Subgroup analysis did not suggest benefit with any particular fractionation scheme.

- Metastases at two years
- 4.2 Metastases at two years with cancer of the uterine cervix (comparison 9, outcome 01)
- Three trials reported this outcome (Fletcher 1977; Glassburn 1974; Watson 1978), involving 522 subjects (23%) of the total subjects in this review), with 251 (48%) allocated to HBO and 271 (52%) to control. There were no withdrawals or losses to folow-up. There was no significant reduction in the incidence of metastases following radiation therapy with HBO (RR 1.05, 0.84 to 1.31, P = 0.70).

- 4.3 Metastases at two years with cancer of the urinary bladder (comparison 9, outcome 02)
- Two trials reported this outcome (Cade 1967; Plenk 1972), involving 80 subjects (2%) of the total subjects in this review, with 25 (51%) allocated to HBO and 24 (49%) to control. However, Plenk 1972 reported no patients with metastases and so did not contribute to the analysis. There were no withdrawals or losses to folow-up. There was no significant difference in the incidence of metastases following radiation therapy with HBO (RR 2.00, 95%CI 0.58 to 6.91, P = 0.27).

- 4.4 Metastases at two years with cancer of the bronchus (comparison 9, outcome 03)
- One trial reported this outcome (Cade 1967), involving 49 subjects (3.5%) of the total subjects in this review, with 39 (51%) allocated to HBO and 41 (49%) to control. There were no withdrawals or losses to folow-up. There was no significant difference in the incidence of metastases following radiation therapy with HBO (RR 1.04, 95%CI 0.60 to 1.80, P = 0.89).

- Metastases at five years
- 4.5 Metastases at five years with cancer of the head and neck (comparison 10, outcome 01)
- One trial reported this outcome (Chang 1973), involving 50 subjects (2%) of the total subjects in this review, with 26 (52%) allocated to HBO and 24 (48%) to control. There were no withdrawals or losses to folow-up. There was no significant reduction in the incidence of metastases following radiation therapy with HBO (RR 0.46, 95%CI 0.09 to 2.30, P = 0.34).

- 4.6 Metastases at five years with cancer of the uterine cervix (comparison 10, outcomes 02, 03, 04)
- Three trials reported this outcome (Brady 1981; Ward 1979; Watson 1978), reporting on 456 subjects after exclusion of withdrawals, 20% of the total subjects in this review, with

221 (49%) allocated to HBOT and 235 (51%) to control. Watson 1978 contributes 83% of the weight of this analysis. Over all fractionation schemes there was no significant difference in the incidence of metastases following radiation therapy with HBO (RR 0.79, 0.50 to 1.26, P = 0.32). Subgroup analysis by fractionation scheme suggests there may be a benefit when comparing 12 or fewer fractions in each group (RR 0.67, 95% CI 0.45 to 0.99, P = 0.05), but not for other comparisons (RR with 12 or fewer fractions with HBO versus more than 12 with control RR 0.07, 95% CI 0.00 to 1.12, P = 0.06 and RR for more than 12 fractions in each group 0.99, 95%CI 0.78 to 1.26, P = 0.95). There was evidence of considerable heterogeneity between trials overall (I2 = 58%) and this result is achieved using a random effects model.

The risk of recurrence was not sensitive to the allocation of those lost to follow-up (best case scenario RR 0.76, 95% CI 0.46 to 1.26, P = 0.28; worst case RR 0.85, 95% CI 0.56 to 1.31, P = 0.46).

5. Adverse effects

- 5.1 Death from radiation tissue effects (comparison 11, outcome 01)
- Two trials reported this outcome (Dische 1999; Watson 1978), reporting on 633 subjects after exclusion of withdrawals (28%) of the total subjects in this review, with 307 (49%) allocated to HBO and 326 (51%) to control. There was no significant increase in the chance of death due to radiation tissue injury following HBO (RR 1.64, 95% CI 0.89 to 3.03, P = 0.11).

- 5.2 Severe radiation tissue injury (comparison 11, outcomes 02, 03, 04)
- Seven trials reported this outcome (Brady 1981; Haffty 1999; Henk 1986; Sause 1979; Sealy 1986; Watson 1978; Ward 1979), reporting on 779 subjects after exclusion of withdrawals (34%) of the total subjects in this review, with 379 (48%) allocated to HBO and 400 (52%) to control. There was a statistically significant increase in the chance of severe radiation tissue injury following HBO (RR 2.35, 95% CI 1.66 to 3.33, P < 0.00001). There was little heterogeneity between trials overall (I2 =15%) and this result is achieved using a fixed effects model. There is an absolute risk increase of 12% when using HBOT (NNH to cause one severe injury is 8, 95% CI 4 to 15).

The increased risk of injury is not sensitive to the allocation of withdrawals (best case scenario RR 1.94, 95% CI 1.39 to 2.69, P < 0.0001; worst case RR 2.69, 95% CI 1.92 to 3.77, P < 0.00001).

- 5.3 Acute central nervous system toxicity (comparison 11, outcome 05, 06, 07)
- Four trials reported this outcome (Cade 1967; Chang 1973; Plenk 1972; Sealy 1986), reporting on 331 subjects after exclusion of withdrawals (15%) of the total subjects in this review, with 150 (45%) allocated to HBO and 181(55%) to control. There was a statistically significant increase in the chance of severe radiation tissue injury following HBO (RR 6.76, 95% CI 1.16 to 39.3, P = 0.03). There was no evidence of important heterogeneity between trials overall (I2 = 0%) and this result is achieved using a fixed effects model. There is an absolute risk increase of 5% when using HBOT (NNH to cause one episode is 22, 95% CI 11 to 44).
- The increased risk of injury is sensitive to the allocation of withdrawals (best case scenario RR 3.00, 95% CI 0.81 to 11.10, P = 0.1; worst case RR 9.74, 95% CI 1.73 to 54.98, P = 0.01).

- 5.4 Middle ear barotrauma (comparison 11, 06)
- Only one trial reported this outcome (Cade 1967), involving 89 subjects (4%) of the total subjects in this review, with 45 allocated to HBO and 44 to control. There were no losses to follow-up or withdrawals. The chance of suffering middle ear barotrauma was not statistically significantly increased with HBO (RR 6.85, 95% CI 0.36 to 128.83, P = 0.20).

Discussion

This review has included data from 19 trials investigating the treatment of various malignancies with radiation therapy while breathing HBO, and we believe these represent all randomised human trials in this area, both published and unpublished, at the time of searching the databases. Ten trials included subjects with head and neck cancers, seven trials carcinoma of the uterine cervix, five carcinoma of the urinary bladder and one each with carcinoma of the brochus, glioblastoma, cancer of the oesophagus and cancer of the rectum. We found some evidence that radiotherapy with HBO reduces one and five year mortality and local tumour recurrence, along with improved early local tumour control for head and neck cancer, and two year local recurrence for carcinoma of the cervix. We also found evidence of significant adverse effects with HBO, particularly the incidence of oxygen toxic seizures and the chance of suffering severe radiation injury. There was no reliable data from these trials to confirm any beneficial effect of HBO for other malignancies studied, nor on the incidence of metastatic disease for cancers of any primary site.

In total, there were 2286 subjects available for evaluation using our planned comparisons. There were 785 subjects with head and neck tumours, 1089 with carcinoma of the cervix and 343 with carcinoma of the bladder. While there were sufficient numbers to form some impression of treatment impact for these tumours, there were only 49 subjects with carcinoma of the bronchus and four each of glioblastoma, carcinoma of the rectum and carcinoma of the oesophagus, therefore the trials in this review have low power to assess the impact of HBO on these tumours. Other major problems for this review were the poor methodological quality of many of these trials, variability in entry criteria and the nature and timing of outcomes, and poor reporting of both outcomes and methodology. In particular, there is a possibility of bias due to different fractionation schemes and radiation doses across the trials, as well as a general failure to report data suitable for comparison of survival over time using the log Hazard Ratio. None of the trials blinded participants, investigators or outcome assessors to treatment.

These trials were published over a 32-year period up to 1999, mainly drawing subjects from the UK and the USA. We had planned to perform subgroup analyses with respect to age, dose of oxygen, dose of radiation therapy and the temporal relationship of the two therapies. After appraisal of these trials however, subgroup analysis was only possible for the different fractionation schemes employed. Specifically, there were no children included and no trials used a sequential approach to HBO and radiation therapy, while the dose of oxygen administered was remarkably uniform per session.

Pooling of data was possible for a number of clinical outcomes of interest, however interpretation of some results is complicated by consideration of fractionation scheme through subgroup analysis. For head and neck cancer, there was an overall reduction in the risk of dying at both one year and five years after therapy (RR 0.83, P = 0.03, NNT = 11 and RR 0.82, P = 0.03, NNT = 5 respectively), and evidence of improved local tumour control immediately following irradiation (RR with HBO 0.58, P = 0.006, NNT = 7). For mortality however, at both times this difference largely reflected an advantage when comparing a small number of fractions while breathing HBOT (less than 12) versus the more standard scheme of 20 to 25 fractions breathing air. When considering only the comparison between all subjects who received fewer than 12 fractions in each group, there is no advantage of HBO (RR at one year 0.93, P = 0.53; five years 0.96, 9, P = 0.73). Any possible benefit of HBO must therefore be interpreted in the knowledge of the most effective fractionation scheme in air. If there is a mortality benefit from reduction in fractionation scheme alone, then HBO may not contribute to this benefit. Our results must, therefore be interpreted with caution. There was no evidence of benefit with respect to mortality or early tumour control for other anatomical sites.

These trials also suggest an advantage following HBO in the chance of experiencing local tumour recurrence at one year (head and neck, RR 0.66, P < 0.0001, NNT = 5), two years (uterine cervix RR 0.60, P = 0.04, NNT = 5) and five years (head and neck (RR 0.77, P = 0.01, NNT = 6), but no such advantage in the incidence of metastatic disease for any anatomical site at any time. Any advantage of the combined therapy seems to be achieved at the cost of some adverse effects. Although the chance of dying from severe radiation injury is not signficantly

increased (RR 1.64, P = 0.11), there was a significant increase in the rate of both severe radiation tissue injury (RR 2.35, P < 0.0001, NNH = 8) and the chance of seizures during therapy (RR 6.76, P = 0.03, NNH 22).

All of these findings are subject to a potential publication bias. While we have made every effort to locate further unpublished data, it remains possible that this review is subject to a positive publication bias, with generally favourable trials more likely to achieve reporting. With regard to any effect on the QOL for these patients, we have located little relevant data.

Reviewers' conclusions

Implications for practice

There is some evidence that HBO improves local tumour control and mortality for cancers of the head and neck, as well as reducing the chance of local tumour recurrence in cancers of the head, neck and uterine cervix. There is however, also some evidence that these outcomes may be related to the use of unusual fractionation schemes, and these benefits should be interpreted with caution. HBO also appears to be associated with significant adverse effects including oxygen toxic seizures and severe tissue radiation injury. Thus, the routine use of HBO in these patients cannot be justified by this review. The methodological and reporting inadequacies of the primary studies included in this review demand a cautious interpretation.

Implications for research

Given the findings of improved tumour control and mortality with the use of HBO for patients with cancers of the head, neck and uterine cervix, there is a case for large randomised trials of high methodological rigour in order to define the true extent of benefit (if any) from the administration of HBO for these cancers at appropriate fractionations schemes. Specifically, such trials must employ appropriate fractionation schemes in both arms in order to clearly define any benefits of HBO as opposed to novel fractionation. The effect of differing oxygen dosage and effect of other therapies administered simultaneously is not known. Any future trials would need to consider in particular:

- appropriate sample sizes with power to detect expected differences
- careful definition and selection of target patients
- appropriate range of oxygen doses per treatment session (pressure and time)
- use of an effective sham therapy where appropriate and ethical
- effective and explicit blinding of outcome assessors
- appropriate outcome measures including all those listed in this review
- careful elucidation of any adverse effects
- the cost-utility of the therapy.

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Potential conflict of interest

None known. Michael Bennett is a hyperbaric physician who regularly treats patients with late radiation tissue injury, while John Feldmeier has previous hyperbaric experience. Chris Milross, John Feldmeier and Robert Smee are radiation oncologists who refer patients with late radiation tissue injury for hyperbaric oxygen therapy (HBOT).

Tables

Characteristics of included studies

Study	Berry 1979
Methods	RCT with allocation concealment and randomisation through central sealed envelope allocation. Patient, outcome assessors and treating team all aware of allocation at the start of treatment. No indication of power calculation.
Participants	24 adults with SCC of the head and neck where radiotherapy was the treatment of choice. 11 allocated to HBOT and 13 to control. No dropouts, but two participants crossed from HBOT to control after refusing HBOT.
Interventions	Control: Between 4450 and 5500 rads in 15 or 20 fractions over 3 weeks.HBOT: 400 to 4500 rads in 10 fractions over 3 weeks, pressure and time not specified but likely to have been 3ATA for 30 to 40 minutes total exposure time.
Outcomes	Death at 1 and 5 years, local recurrence at 5 years.
Notes	Also see Berry 1968.Schulz rating: Randomisation A, Allocation concealment A, selection bias B, blinding C
Allocation concealment	A
Study	Brady 1981
Methods	RCT with allocation concealment not clear, method of randomisation not stated. Patient, outcome assessors and treating team all aware of allocation. No indication of power calculation.
Participants	65 adults with Stage IIb to IVa carcinoma of the uterine cervix where radiotherapy was the treatment of choice. 34 allocated to HBOT and 31 to control. Several participants refused HBOT and there were only 19 of 34 available for analysis in HBOT group and 29 of 31 in the control.
Interventions	Control: 5000 rads by external beam in 25 fractions over five weeks plus radium implants where possible. HBOT: 4000 rads in 10 fractions over five weeks with intracavitary implants where possible. All external beam radiotherapy conducted at 3ATA breathing 100% oxygen, total compression time about 40 minutes.
Outcomes	Death at 4 years, local recurrence at 4 years, metastases at 4 years, late radiation tissue injuries.
Notes	Trial stopped due to poor accrual. Schulz rating: Randomisation C, Allocation concealment B, selection bias C, blinding C
Allocation concealment	B
Study	Cade 1967
Methods	RCT with allocation concealment and randomisation by centrally generated card method . Two separate studies reported - one for

	carcinoma of the bronchus and one for carcinoma of the urinary bladder. Patient, outcome assessors and treating team all aware of allocation at start of therapy course. No indication of power calculation.
Participants	Trial 1: 49 adults with carcinoma of the bronchus, 25 allocated to HBOT and 24 to control.Trial 2: 40 adults with carcinoma of the urinary bladder with spread confined to the pelvis, 20 allocated to each of HBOT and control. No drop-outs or losses to follow-up in either trial.
Interventions	Control: 6000 rads by external beam in 40 fractions over eight weeks.HBOT: Identical radiotherapy schedule conducted at 3ATA breathing 100% oxygen, total compression time about 40 minutes.
Outcomes	Death 1 year, metastatic disease 1 to 2 years, oxygen toxicity data (combined for both trials).
Notes	Also reported in McEwen 1968.Schulz rating: Randomisation A, Allocation concealment A, selection bias A, blinding C
Allocation concealment	A
Study	Cade 1978
Methods	Mulitcentred RCT with allocation concealment and randomisation by centrally generated envelope method . Patient, outcome assessors and treating team all aware of allocation at start of therapy course. No indication of power calculation.
Participants	241 adults with carcinoma of the urinary bladder spread to vagina or rectum. Losses not accounted for, final analysis 118 in each group (5 lost).
Interventions	Different regimens of treatment were used in each of the four centres and also varied within some centres during the course of the trial. No individual centre or fractionation data is given.Control: 1A. (Portsmouth 65p) 6000 rads in 40 fractions over 8 weeks, 1B. (Portsmouth 57p) 3600 rads in 6 fractions over 2.5 weeks. 2. (Oxford 25p) 4250 rads in 10 fractions 4.5 weeks. 3. (Glasgow 27p) 4500 rads in 24 fractions over 7 weeks. 4A. (Mount Vernon 41p) 6000 rads in 30 fractions over 6 weeks, 4B. (Mount Vernon 26p) 4725 rads in 15 fractions over 4.5 weeks. HBOT: Same regimen, with all external beam radiotherapy conducted while breathing 100% oxygen at 3ATA for approximately 30 minutes.
Outcomes	Death at 1 and 5 years.
Notes	Also see Kirk 1976, Wiernik 1974 and Dische 1973.Schulz rating: Randomisation A, Allocation concealment A, selection bias B, blinding C
Allocation concealment	A
Study	Chang 1973
Methods	RCT with allocation concealment and randomisation through sealed

	envelope method. Patient, outcome assessors and treating team all aware of allocation at the start of treatment. No indication of power calculation.
Participants	51 previously untreated adults with advanced (T3 and T4) carcinomas of the soft palate and adjacent structures. 26 allocated to HBOT and 25 to control. No dropouts or losses to analysis.
Interventions	Control: Two regimens. 1. 6000 rads in 30 fractions over 6 weeks. 2. 4200 rads in 7 fractions over 3.5 weeks.HBOT: 3600 rads in 6 fractions over 3 weeks while breathing 100% oxygen at 3ATA for approximately 30 minutes.
Outcomes	Death at 1 and 5 years, early local tumour control, metastatic disease 5 years, oxygen toxicity. HBOT group results split beween the two controls for analysis.
Notes	Schulz rating: Randomisation A, Allocation concealment B, selection bias A, blinding C
Allocation concealment	B
Study	Dische 1999
Methods	RCT with allocation concealment and randomisation by centrally generated envelope method . Patient, outcome assessors and treating team all aware of allocation. No indication of power calculation.
Participants	335 adults with Stage IIb or III carcinoma of the uterine cervix where radiotherapy was the treatment of choice. 146 allocated to HBOT and 170 to control. 19 participants lost to follow-up and group not indicated.
Interventions	Four different treatment regimens used. Where individual centre data is given it is used in analysis.Control: 1. (88 partcipants) 4500 rads in 10 fractions over 5 weeks. 2. (82 p) 5800 rads in 27 fractions over 5.5 weeks. Some patients also had intra-cavitary treatment.HBOT: Two groups received the same radiotherapy but while at 3ATA breathing oxygen for approximately 30 minutes.
Outcomes	Death 1 and 5 years, locoregional control 1 and 5 years, death by late radiation effects 5 years.
Notes	See also Bennett 1977. 27 fraction HBOT schema discontinued after interim analysis did not suggest any benefit.Schulz rating: Randomisation A, Allocation concealment A, selection bias B, blinding C
Allocation concealment	A
Study	Fletcher 1977
Methods	RCT stratified for node involvement and clinical stage, with allocation concealment not clear, method of randomisation not stated. Patient, outcome assessors and treating team all aware of allocation. No indication of power calculation.
Participants	233 adults with Stage IIb to IVa carcinoma of the uterine cervix where

	radiotherapy was the treatment of choice. 109 allocated to HBOT and 124 to control. No dropouts or losses to follow-up.
Interventions	Control: between 4000 and 5500 rads by external beam in 20 to 35 fractions over four to five weeks plus radium implant in more advanced cases. HBOT: Same regimen, with all external beam radiotherapy conducted at 3ATA breathing 100% oxygen, total compression time about 40 minutes.
Outcomes	Death at 2 years, metastatic disease 2 years
Notes	An interim report that does not seem to have been reported in a complete paper to date. Also see Lindberg 1973 and Fletcher 1975.Schulz rating: Randomisation C, Allocation concealment B, selection bias A, blinding C
Allocation concealment	B
Study	Glassburn 1974
Methods	RCT with allocation concealment not clear, method of randomisation not stated. Patient, outcome assessors and treating team all aware of allocation. No indication of power calculation. Participants excluded if second primary , prior radiotherapy or contraindication to HBOT
Participants	40 adults with Stage III or IV carcinoma of the uterine cervix where radiotherapy was the treatment of choice. 17 allocated to HBOT and 23 to control. No dropouts or losses to follow-up.
Interventions	Control: 6000 external beam in 24 fractions over six weeks plus radium implant. HBOT: Same regimen, but dose reduced by 7% after first six partcipants displayed high rate of gastrointestinal complications. All external beam radiotherapy conducted at 3ATA breathing 100% oxygen, total compression time about 40 minutes.
Outcomes	Death at 27 months, local tumour recurrence 27 months, metastases at 27 months
Notes	An interim report that does not seem to have been reported in a còmplete paper to date. Also see Faust 1969.Schulz rating: Randomisation C, Allocation concealment B, selection bias A, blinding C
Allocation concealment	B
Study	Haffty 1999
Methods	RCT using sealed envelopes but allocation concealment not clear. Patient, outcome assessors and treating team all aware of allocation after start of therapy.
Participants	48 adults with SCC of the head and neck where radiotherapy was the treatment of choice. 23 allocated to HBOT and 25 to control.
Interventions	Control: 2530 rads in 2 fractions over 2 weeks.HBOT: 2300 rads in 2 fractions over 2 weeks, while anaesthetised and intubated breathing 100% oxygen at 4ATA for 30 to 40 minutes total exposure time.
Outcomes	Death at 1, 2 and 5 years, local tumour control, recurrence rate,

	complications
Notes	Very unusual radiation regimen.Schulz rating: Randomisation A, Allocation concealment B, selection bias A, blinding C
Allocation concealment	B
Study	Henk 1977a
Methods	RCT stratified by site of tumour (nasal and oral, laryngeal, laryngopharyngeal and other) with allocation concealment not clear, method of randomisation not stated. Patient, outcome assessors and treating team all aware of allocation. No indication of power calculation.
Participants	295 adults with SCC of the head and neck where radiotherapy was the treatment of choice. 143 allocated to HBOT and 152 to control. Dropouts identified (18 from HBOT group, 1 from control) but not included in analysis.
Interventions	Control: Between 3500 and 4500 rads in 10 fractions over 3 weeks.HBOT: Same regimen, pressure and time not specified but likely to have been 3ATA for 30 to 40 minutes total exposure time.
Outcomes	Death at 1 to 5 years, local control of tumour at 3 months, local recurrence rates 1 to 5 years, significant radiation tissue effects at 6 months
Notes	Other reports of this trial in Henk 1974, Henk 1975, Kunkler 1968Schulz rating: Randomisation C, Allocation concealment B, selection bias B, blinding C
Allocation concealment	B
Study	Henk 1986
Methods	RCT stratified by site of tumour (mouth, oropharynx, nasal sinus, nasopharynx, larynx, hypopharynx and middle ear). Allocation concealement and randomisation achieved by centrally supplied sealed envelopes. Patient, outcome assessors and treating team all aware of allocation after trial started. No indication of power calculation.
Participants	107 adults with SCC of the head and neck where radiotherapy was the treatment of choice. 54 allocated to HBOT and 53 to control. Dropouts identified (1 from HBOT group) but not included in analysis.
Interventions	Control: 6400 rads in 30 fractions over 6 weeks.HBOT: 4100 rads in 10 fractions over 3 weeks, pressure and time not specified but likely to have been 3ATA for 30 to 40 minutes total exposure time.
Outcomes	Death at 1 and 5 years, recurrence at 1 and 4 years, late radiation tissue effects at 5 years.
Notes	Other reports of this trial in Henk 1974, Henk 1975, Henk 1977Schulz rating: Randomisation A, Allocation concealment A, selection bias A, blinding C
Allocation concealment	A

Study	Plenk 1972
Methods	RCT using random number table, allocation concealment not clear. Patient, outcome assessors and treating team all aware of allocation. No indication of power calculation.
Participants	40 adults with carcinoma of the urinary bladder. 19 allocated to HBOT and 21 to control. More than 50% loss to follow-up at two years.
Interventions	Control: 6000 rads in 24 to 30 fractionsover six weeks.HBOT: 4800 rads in 12 fractions over about four weeks at 3ATA breathing oxygen for about 40 minutes.
Outcomes	Death at one and two years, oxygen toxicity.
Notes	Schulz rating: Randomisation A, Allocation concealment B, selection bias C, blinding C
Allocation concealment	B
Study	Sause 1979
Methods	RCT of previously untreated heaad and neck SCC with allocation concealment not clear, method of randomisation not stated. Patient, outcome assessors and treating team all aware of allocation. No indication of power calculation.
Participants	50 adults with SCC of the head and neck where radiotherapy was the treatment of choice. Group allocation unclear but six dropouts and 21 analysed in HBOT group, 23 in control.
Interventions	Control: Total dose 6250 rads in 25 fractions over 6 weeks.HBOT: Total dose 4800 rads in 12 fractions over 5 weeks while breathing oxygen at 3ATA for about 30 minutes.
Outcomes	Death at 2-8 years, local tumour control and late radiation tissue injury.
Notes	5 partici[pants excluded from analysis because they died from 'intercurrent disease' prior to 2 year folow-up.Schulz rating: Randomisation C, Allocation concealment B, selection bias B, blinding C
Allocation concealment	B
Study	Sealy 1986
Methods	RCT stratified by sex, site of tumour, extent of node involvement and histology. Allocation concealment achieved by sealed envelopes prepared by an individual not otherwise involved in the study. Patient, outcome assessors and treating team all aware of allocation. No indication of power calculation.
Participants	130 adults with SCC of the mouth or fixed lymph nodes in the neck where radiotherapy was the treatment of choice. 64 allocated to HBOT and 66 to control. Dropouts identified (4 from HBOT group, 2 from control) but not included in analysis.
Interventions	Control: 6300 rads in 30 fractions over 6 weeks.HBOT: 3600 rads in 6

	fractions over 2.5 weeks at 3ATA for 30 to 40 minutes total exposure time, plus misonidazole 2 grams per square metre body surface at the time of each fraction.
Outcomes	Death at one and two years, local recurrence at one year, toxic reactions to therapy and oxygen toxicity.
Notes	Other report of this trial in Sealy 1978.Schulz rating: Randomisation B, Allocation concealment A, selection bias B, blinding C
Allocation concealment	A
Study	Shigematsu 1973
Methods	RCT stratified by tumour stage and possibly allocation was actually achieved by quasi-random method. No indication of allocation concealment. Patient, outcome assessors and treating team all aware of allocation after treatment started. No indication of power calculation.
Participants	42 adults with SCC of the maxillary sinus. 21 allocated to both HBOT and control. No drop-outs from therapy or losses to follow-up. All patients had myringotomies prior to compression.
Interventions	Control: 6000 to 7000 rads 8 or 10 fractions over 4 to 5 weeks.HBOT: 4000 to 5000 rads on the same schedule at 3ATA for 20 to 30 minutes total exposure time.
Outcomes	Death at one year, local early tumour control, recurrence at one year
Notes	Schulz rating: Randomisation C, Allocation concealment B, selection bias A, blinding C
Allocation concealment	B
Study	Tobin 1971
Methods	RCT with randomisation by card drawn by an individual not involved with the study. Allocation probably made in a concealed manner after randomisation. Patient, outcome assessors and treating team all aware of allocation after trial started. No indication of power calculation. Several different tumours studied: head and neck, uterine cervix, urinary bladder, rectal, brain and oesophagus.
Participants	Group 1: 17 adults with carcinoma of the head and neck, 9 allocated to HBOT and 8 to control.Group 2: 14 adults with carcinoma of the uterine cervix, 7 allocated to both HBOT and control.Group 3. 6 adults with carcinoma of the urinary bladder, 3 allocated to each of HBOT and control. Group 4. 4 adults with cadenocarcinoma of the rectum, 2 allocated to each of HBOT and control.Group 5. 4 adults with glioblastoma of the brain, 2 allocated to each of HBOT and control.Group 6. 4 adults with carcinoma of the oesophagus, 2 allocated to each of HBOT and control.A further three patients allocated to HBOT were incomplete when trial ceased and have not been analysed.
Interventions	Control: Exact dose and fractionation schedules not given, but 'normal fractionation implies 24 to 30 fractions over six weeks approximately and varied with tumour site. HBOT: Same regimen, conducted at

	3ATA breathing 100% oxygen, total compression time about 50 minutes.
Outcomes	Death at 1 and 2 years.
Notes	Trial terminated after explosive decompression of the chamber due to degradation of chamber wall from radiation.Schulz rating: Randomisation B, Allocation concealment A, selection bias A, blinding C
Allocation concealment	A
Study	Van Den Brenk 1968
Methods	Pseudo-randomised controlled trial with allocation to group by birth date. No allocation concealment. Two separate studies reported - one for carcinoma of the head and neck and one for carcinoma of the urinary bladder. Patient, outcome assessors and treating team all aware of allocation. No indication of power calculation.
Participants	Trial 1: 29 adults with carcinomas of the head and neck, 17 allocated to HBOT and 12 to control.Trial 2: 16 adults with carcinoma of the urinary bladder, 8 allocated to each of HBOT and control. No drop-outs or losses to follow-up in either trial.
Interventions	Control: Trial 1. 3100 rads in 4 fractions . Trial 2. 3300 rads in 6 fractions.HBOT: Trial 1. 2,900 rads in 4 fractions. Trial 2. 3000 rads in 6 fractions Both conducted at 3ATA breathing 100% oxygen, total compression time about 40 minutes.
Outcomes	Death at 6 months, local tumour control early.
Notes	Schulz rating: Randomisation C, Allocation concealment C, selection bias A, blinding C
Allocation concealment	C
Study	Ward 1979
Methods	RCT with allocation concealment and randomisation by centrally generated envelope method . Patient, outcome assessors and treating team all aware of allocation. No indication of power calculation.
Participants	82 adults with Stage IIb or III carcinoma of the uterine cervix where radiotherapy was the treatment of choice. 39 allocated to HBOT and 43 to control. Four dropouts not analysed because treatment incomplete plus five participants crossed over from HBOT to control group when they refused HBOT.
Interventions	Control: 3150 rads external beam in 10 fractions over two weeks plus three cathetron rod placements of 950 rads each over six weeks. HBOT: Same regimen, All external beam radiotherapy conducted at 3ATA breathing 100% oxygen, total compression time about 30 minutes.
Outcomes	Death at 1 and 5 years, local recurrence at 1 and 5 years, metastatic disease at 5 years, radiation tissue injury .
Notes	Also see Ward 1978, 1973 and 1974.Schulz rating: Randomisation A,

	Allocation concealment A, selection bias C, blinding C
Allocation concealment	A
Study	Watson 1978
Methods	Mulitcentred RCT with allocation concealment and randomisation by centrally generated envelope method . Patient, outcome assessors and treating team all aware of allocation at start of therapy course. No indication of power calculation.
Participants	320 adults with Stage III to IVa carcinoma of the uterine cervix where radiotherapy was the treatment of choice. 161 allocated to HBOT and 159 to control. No dropouts or losses to follow-up.
Interventions	Different regimens of treatment were used in each of the four centres. Where individual centre data is given it is used in analysis.Control: 1. (Portsmouth 37p) 3600 rads over 6 or 7 fractions in 3 weeks. 2. (Oxford 34p) 4250 rads in 10 fractions 4.5 weeks. 3. (Glasgow 162p) 4500 rads in 20 fractions over 4 weeks. 4. (Mount Vernon 87p) 5500 rads in 27 fractions over 6 weeks. All but group 1. had radium insertion. HBOT: Same regimen, with all external beam radiotherapy conducted while breathing 100% oxygen at unknown pressure and duration.
Outcomes	Death at 1, 2 and 5 years, local recurrence at 5 years, metastatic disease at 1 and 5 years, late radiation tissue effects and severe tissue reactions.
Notes	Also see Wiernik 1974 and Dische 1974.Schulz rating: Randomisation A, Allocation concealment A, selection bias A, blinding C
Allocation concealment	A

ATA - Atmospheres absolute
HBOT - Hyperbaric oxygen therapy
RCT - Randomised controlled trial
Rads -
SCC - Squamous cell carcinoma

Characteristics of excluded studies

Study	Reason for exclusion
Bennett 1977	More fully reported in Dische 1999
Berry 1968	More fully reported in Berry 1979 and Ward 1979
Dische 1973	More fully reported in Cade 1978
Dische 1974	More fully reported in Watson 1978
Dische 1979	A summary of several trials with no new data
Dische 1991	A summary of several trials with no new data
Faust 1970	More fully reported in Glassburn 1974
Fletcher 1975	More fully reported in Fletcher 1977

Henk 1974	More fully reported in Henk 1977a and Henk 1986
Henk 1975	More fully reported in Henk 1977a and Henk 1986
Henk 1977b	More fully reported in Henk 1986
Kirk 1976	More fully reported in Cade 1978
Kunkler 1968	More fully reported in Henk 1977a
Lindberg 1973	More fully reported in Fletcher 1977
MRCWP 1978	Summary of trials with no new data
McEwen 1968	More fully reported in Cade 1967
McEwen 1972	More fully reported in Cade 1967
Sealy 1978	More fully reported in Sealy 1986
Ward 1973	More fully reported in Ward 1979
Ward 1974	More fully reported in Ward 1979
Ward 1978	More fully reported in Ward 1979
Wiernik 1973	More fully reported in Watson 1978 and Cade 1978

Additional tables

Table 01 Search strategy

EMBASE	MEDLINE (OVID)
1. exp hyperbaric oxygen/ 2. (high adj5 (pressur$ or oxygen$)).mp. 3. hyperbaric$.mp. 4. 2 or 3 5. oxygen$.mp. 6. 4 and 5 7. (HBO or HBOT).mp. 8. multiplace chamber$.mp. 9. monoplace chamber$.mp. 10. 1 or 6 or 7 or 8 or 9 11. exp radiation/ 12. (radiation$ or radiotherap$ or late$ or damag$ or wound$ or destruction$ or oedema$ or edema$ or fracture$).mp 13. 11 or 12 14. 11 or 13 15. exp radiotherapy/ 16. 14 or 15 18. 10 and 16	1. hyperbari$.tw 2. hbo$.tw 3. mutliplace chamber.tw 4. monoplace chamber.tw 5. or/1-4 6. exp Radiotherapy 7. radio$.tw 8. or/6-7 9. 5 and 8

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Graphs

Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

01 Death at one year				
Outcome title	No. of	No. of	Statistical method	Effect size

	studies	participants		
01 Head and neck cancer	10	710	Relative Risk (Random) 95% CI	0.83 [0.70, 0.98]
02 Head and neck - best case scenario	10	743	Relative Risk (Random) 95% CI	0.73 [0.62, 0.85]
03 Head and neck - worst case scenario	10	743	Relative Risk (Random) 95% CI	0.93 [0.76, 1.15]
04 Uterine cervix cancer	6	728	Relative Risk (Fixed) 95% CI	0.88 [0.69, 1.11]
05 Uterine cervix - best case scenario	4	732	Relative Risk (Fixed) 95% CI	0.87 [0.69, 1.10]
06 Uterine cervix - worst case scenario	4	732	Relative Risk (Fixed) 95% CI	0.91 [0.72, 1.15]
07 Urinary bladder cancer	4	330	Relative Risk (Fixed) 95% CI	0.97 [0.74, 1.27]
08 Urinary bladder - best case scenario	4	337	Relative Risk (Fixed) 95% CI	0.92 [0.71, 1.21]
09 Urinary bladder - worst case scenario	4	337	Relative Risk (Fixed) 95% CI	1.03 [0.78, 1.34]
10 Bronchial cancer	1	49	Relative Risk (Fixed) 95% CI	1.09 [0.72, 1.64]
11 Rectal cancer	1	4	Relative Risk (Fixed) 95% CI	2.00 [0.50, 8.00]
12 Oesphageal cancer	1	4	Relative Risk (Fixed) 95% CI	0.50 [0.13, 2.00]
13 Gliobastoma	1	4	Relative Risk (Fixed) 95% CI	Not estimable

02 Death at two years

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Head and neck cancer	3	189	Relative Risk (Fixed) 95% CI	0.97 [0.83, 1.12]
02 Head and neck - best case scenario	3	195	Relative Risk (Fixed) 95% CI	0.92 [0.79, 1.07]
03 Head and neck - worst case scenario	3	195	Relative Risk (Fixed) 95% CI	1.00 [0.86, 1.15]
04 Uterine cervix cancer	5	607	Relative Risk (Random) 95% CI	0.94 [0.76, 1.15]
05 Urinary bladder carcinoma	2	24	Relative Risk (Fixed) 95% CI	1.67 [0.64, 4.33]
06 Urinary bladder - best case	2	58	Relative Risk (Random) 95% CI	0.47 [0.04, 5.25]

07 Urinary bladder - worst case	2	58	Relative Risk (Fixed) 95% CI	5.70 [2.26, 14.37]

03 Death at five years

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Head and neck cancer	7	550	Relative Risk (Fixed) 95% CI	0.82 [0.69, 0.98]
02 Head and neck - best case scenario	7	575	Relative Risk (Fixed) 95% CI	0.77 [0.64, 0.92]
03 Head and neck - worst case scenario	7	575	Relative Risk (Fixed) 95% CI	0.96 [0.81, 1.13]
04 Uterine cervix cancer	6	772	Relative Risk (Random) 95% CI	0.95 [0.80, 1.14]
05 Uterine cancer - best case scenario	6	783	Relative Risk (Random) 95% CI	0.92 [0.77, 1.09]
06 Uterine cancer - worst case scenario	6	783	Relative Risk (Random) 95% CI	0.98 [0.81, 1.18]
07 Urinary bladder cancer	1	236	Relative Risk (Fixed) 95% CI	1.04 [0.88, 1.22]

04 Failure to control local tumour at three months

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Head and neck cancer	6	446	Relative Risk (Random) 95% CI	0.58 [0.39, 0.85]
02 Head and neck cancer - best case scenario	6	465	Relative Risk (Random) 95% CI	0.57 [0.41, 0.78]
03 Head and neck - worst case scenario	6	465	Relative Risk (Random) 95% CI	0.59 [0.35, 1.00]

05 Local recurrence at one year

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Head and neck cancer	5	582	Relative Risk (Fixed) 95% CI	0.66 [0.56, 0.78]
02 Head and neck cancer - best case scenario	5	611	Relative Risk (Fixed) 95% CI	0.61 [0.51, 0.71]
03 Head and neck cancer - worst case scenario	5	611	Relative Risk (Fixed) 95% CI	0.75 [0.65, 0.87]
04 Uterine cervix cancer	5	714	Relative Risk (Random) 95% CI	0.82 [0.63, 1.06]
05 Uterine cervix cancer - best case scenario	5	718	Relative Risk (Random) 95% CI	0.81 [0.63, 1.02]
06 Uterine cervix cancer -	5	718	Relative Risk	0.87 [0.63,

worst case scenario			(Random) 95% CI	1.19]

06 Local recurrence at two years

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Head and neck cancer	1	48	Relative Risk (Fixed) 95% CI	0.83 [0.60, 1.14]
02 Uterine cervix cancer	3	360	Relative Risk (Random) 95% CI	0.60 [0.38, 0.97]

07 Local recurrence at five years

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Head and neck cancer	5	495	Relative Risk (Random) 95% CI	0.77 [0.62, 0.95]
02 Head and neck cancer - best case scenario	5	521	Relative Risk (Random) 95% CI	0.70 [0.57, 0.86]
03 Head and neck cancer - worst case scenario	5	521	Relative Risk (Random) 95% CI	0.84 [0.66, 1.06]
04 Uterine cervix cancer	6	772	Relative Risk (Random) 95% CI	0.85 [0.65, 1.13]
05 Uterine cervix cancer - best case scenario	6	783	Relative Risk (Fixed) 95% CI	0.83 [0.72, 0.97]
06 Uterine cervix cancer - worst case scenario	6	783	Relative Risk (Fixed) 95% CI	0.89 [0.76, 1.03]

08 Metastases at one year

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Uterine cervix cancer	2	320	Relative Risk (Fixed) 95% CI	0.79 [0.52, 1.19]

09 Metastases at two years

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Uterine cervix cancer	3	522	Relative Risk (Fixed) 95% CI	1.05 [0.84, 1.31]
02 Urinary bladder carcinoma	2	80	Relative Risk (Fixed) 95% CI	2.00 [0.58, 6.91]
04 Carcinoma of the bronchus	1	49	Relative Risk (Fixed) 95% CI	1.04 [0.60, 1.80]

10 Metastases at five years

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Head and neck carcinoma	1	50	Relative Risk (Fixed) 95% CI	0.46 [0.09, 2.30]

02 Uterine cervix cancer	4	456	Relative Risk (Random) 95% CI	0.79 [0.50, 1.26]
03 Uterine cervix cancer - best case scenario	4	467	Relative Risk (Random) 95% CI	0.76 [0.46, 1.26]
04 Uterine cervix cancer - worst case scenario	4	467	Relative Risk (Random) 95% CI	0.85 [0.56, 1.31]

11 Adverse events

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Death through radiation tissue injury	2	633	Relative Risk (Fixed) 95% CI	1.64 [0.89, 3.03]
02 Severe radiation tissue injury	7	779	Relative Risk (Fixed) 95% CI	2.35 [1.66, 3.33]
03 Severe radiation tissue injury - best case scenario	7	803	Relative Risk (Fixed) 95% CI	1.94 [1.39, 2.69]
04 Severe radiation tissue injury - worst case scenario	7	803	Relative Risk (Fixed) 95% CI	2.69 [1.92, 3.77]
05 Acute central nervous system oxygen toxicity	4	331	Relative Risk (Fixed) 95% CI	6.76 [1.16, 39.31]
06 Acute central nervous system toxicity - best case scenario	4	337	Relative Risk (Fixed) 95% CI	3.00 [0.81, 11.10]
07 Acute central nervous system toxicity - worst case scenario	4	337	Relative Risk (Fixed) 95% CI	9.74 [1.73, 54.99]
10 Middle ear barotrauma	1	89	Relative Risk (Fixed) 95% CI	6.85 [0.36, 128.84]

Cover sheet

Hyperbaric oxygenation for tumour sensitisation to radiotherapy

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Synopsis

Breathing hyperbaric oxygen (HBO) during radiotherapy for cancer treatment may reduce the risk of death and local recurrence within five years for head and neck cancer, and of recurrence within two years for cancer of the cervix.

Breathing HBO involves enclosing patients in a specially designed chamber and it is sometimes used to increase the effect of radiotherapy and thus improve both mortality and tumour regrowth. We found some evidence that people with head and neck cancer are less likely to die

within five years if they are treated this way, and evidence that re-growth of tumour at the original site is less likely for head and neck, and cervical cancer. However, HBO may only be effective when radiotherapy is given in an unusually small number of sessions, each with a relatively high dose. HBO does not appear to work for other cancers studied. Our conclusions are based on 19 randomised trials with over 2000 patients.