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Hyperbaric oxygenation for tumour sensitisation to radiotherapy (Review)

Bennett MH, Feldmeier J, Smee R, Milross C

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[Intervention Review]

Hyperbaric oxygenation for tumour sensitisation to radiotherapy

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ABSTRACT

Background

Cancer is a common disease and radiotherapy is one well-established treatment for some solid tumours. Hyperbaric oxygenation therapy (HBOT) may improve the ability of radiotherapy to kill hypoxic cancer cells, so the administration of radiotherapy while breathing hyperbaric oxygen may result in a reduction in mortality and recurrence.

Objectives

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

Search methods

In March 2011 we searched The Cochrane Central Register of Controlled Trials (CENTRAL), (*The Cochrane Library*, Issue 3), MEDLINE, EMBASE, DORCTHIM and reference lists of articles.

Selection criteria

Randomised and quasi-randomised studies comparing the outcome of malignant tumours following radiation therapy while breathing HBO versus air.

Data collection and analysis

Three review authors independently evaluated the quality of the relevant trials and extracted the data from the included trials.

Main results

Nineteen trials contributed to this review (2286 patients: 1103 allocated to HBOT and 1153 to control). With HBOT, there was a reduction in mortality for head and neck cancers at both one year and five years after therapy (risk ratio (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 HBOT varied with different fractionation schemes. Local tumour recurrence was less likely with HBOT 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). 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 HBOT.

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Authors' conclusions

There is some evidence that HBOT 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. HBOT is associated with significant adverse effects including oxygen toxic seizures and severe tissue radiation injury. The methodological and reporting inadequacies of the studies included 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.

PLAIN LANGUAGE SUMMARY

High pressure oxygen breathing during radiotherapy for cancer treatment

Breathing oxygen while at raised pressure in a closed chamber (hyperbaric oxygen or HBO) may increase the effectiveness of radiotherapy and thus improve mortality and reduce 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 regrowth of tumour at the original site is less likely for head and neck, and cervical cancer. However, Hyperbaric oxygen therapy (HBOT) may only be effective when radiotherapy is given in an unusually small number of sessions, each with a relatively high dose. HBOT does not appear to work for other cancers studied. Our conclusions are based on 19 randomised trials with over 2000 patients.

BACKGROUND

Description of the condition

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 it 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).

Description of the intervention

Hyperbaric oxygen therapy (HBOT) is 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.

How the intervention might work

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 radioresistance 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 randomised 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

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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 (OR) of 0.83 (95% confidence interval (CI) 0.77 to 0.89) (Overgaard 1996). The search strategy, inclusion and 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.

Why it is important to do this review

These decisions were made despite the publication of a number of promising clinical trials with HBO, and it has been suggested HBOT 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 the Overgaard 1996 review, we believe a structured systematic search may reveal further evidence, and we are aware of at least two randomised trials published after 1996 (Dische 1999; Haffty 1999).

HBOT 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). For all these reasons, we believe a review may clarify the true value, if any, of HBOT in this area.

OBJECTIVES

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

1. Does the addition of HBO to radiation therapy:
    i) reduce mortality at any time following therapy?
    ii) increase local tumour response?
    iii) reduce the incidence of local recurrence?
    iv) reduce the incidence of metastatic spread?
    v) improve the quality of life (QoL) 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?

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs that:

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

Types of participants

Patients with solid tumours where radiation therapy is indicated. We did not impose any restrictions on the basis of age or gender.

Types of interventions

We included studies that compared treatment regimens which included HBO with similar regimens that excluded HBO, with or without the use of other sensitisers. Where cointerventions or fractionation regimens differed significantly between studies we clearly stated this and discussed the implications, or performed an appropriate subgroup analysis.

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

Types of outcome measures

Primary outcomes

1. Mortality rate at any time.
2. Complete or partial failure to control local tumour at any time.

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3. Local recurrence rate at any time.
4. Metastatic disease at any time.

Secondary outcomes

1. Quality of life (QoL) assessment.

Adverse effects of HBOT

Specific to combined HBOT/radiation therapy

- Acute tissue reaction in irradiated area.
- Late tissue injury in irradiated area.
- Pain scores.

General relating to HBO

- Visual disturbance (short and long term).
- Barotrauma (aural, sinus, pulmonary in the short and long term).
- Oxygen toxicity (short term).

Any other recorded adverse effects would be reported and discussed.

Search methods for identification of studies

Electronic searches

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

We searched the following (from inception) in November 2004 and then repeated the searches in September 2008 and March 2011 (not CINAHL): Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 1), MEDLINE (week 1, 2011), EMBASE (week 11, 2011), and an additional database developed in our hyperbaric facility (the Database of Randomised Trials in Hyperbaric Medicine, Bennett 2011). We searched CINAHL in 2004 and 2008, but not 2011. The search strategy was broad and the strategies we used are given in Appendix 1, Appendix 2, Appendix 3 and Appendix 4.

Searching other resources

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

- We contacted experts in the field and leading hyperbaric therapy centres (as identified by personal communication and searching the Internet) and asked for additional relevant data in terms of published or unpublished randomised trials.
- We handsearched relevant hyperbaric textbooks (Jain 2009; Kindwall 2008; Mathieu 2006; Neuman 2008), journals (*Undersea and Hyperbaric Medicine*, *Hyperbaric Medicine Review*, *South Pacific Underwater Medicine Society (SPUMS) Journal*, *European Journal of Hyperbaric Medicine and Aviation* and *Space and Environmental Medicine Journal*) and conference proceedings (Undersea and Hyperbaric Medical Society, SPUMS, European Undersea and Baromedical Society and International Congress of Hyperbaric Medicine) published since 1980.
- We contacted authors of relevant studies to request details of unpublished or ongoing investigations.
- We examined the reference list of all trials for inclusion in this review.

We considered all languages. We contacted authors if there was any ambiguity about the published data.

Data collection and analysis

Selection of studies

Two review authors (MB and RS) scanned the records retrieved by the initial search to identify trials that met the inclusion criteria. The same two review authors retrieved and reviewed the full-text articles 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 and management

Two review authors (MB and RS) used standardisation forms to independently extract data from the studies. Extracted data included the following characteristics: methods (number eligible and randomised, adequacy of randomisation, allocation concealment, blinding, and completeness of follow-up); participant characteristics and exclusions; interventions; outcomes (dichotomous variables (number with outcome of interest); and continuous variables (mean and standard deviation). We attempted to contact primary authors when missing data were encountered or if necessary data were not clearly stated. The review authors resolved all differences by discussion.

Assessment of risk of bias in included studies

We assessed study quality by using an adaptation of the method outlined in Schulz 1995. Results from the study quality are presented in a descriptive manner. We assessed the following characteristics.

Adequacy of the randomisation process:

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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 the randomisation 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 randomisation; 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 (ITT) 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.

Sensitivity analysis

We used a fixed-effect model where there was no evidence of significant heterogeneity between studies and a random-effects model when such heterogeneity was likely (DerSimonian 1986). We considered the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. We tested heterogeneity using the I^2 statistic and assumed significant heterogeneity if I^2 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 lgHR and variance (Parmar 1998). For proportions (dichotomous outcomes), we used RR. We would have converted continuous data to the weighted mean difference (WMD) using the inverse variance method and calculated an overall WMD. We tested selection bias using a 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 analyses 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 dose over 12 fractions); and
4. simultaneous versus sequential administration of HBOT.

RESULTS

Description of studies

Results of the search

In our original searches in 2004 and 2008, we identified a combined 106 publications apparently dealing with the use of HBOT in conjunction with therapeutic radiotherapy. A further search (combined strategy with that for a related Cochrane review, 'Hyperbaric oxygen therapy for late radiation tissue injury' (Bennett 2005) update in progress) located another 180 publications. Following identification and deletion of duplicate publications, we culled this list to 226 publications. Initial examination of the titles suggested 123 were not relevant to this review, leaving 103 publications for which we retrieved the abstracts, where available. Examination of the abstracts determined that 60 were not relevant to this review. We retrieved the full reports of the remaining 43 possible comparative trials. After appraisal, we further excluded five 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'). We accepted the remaining 19 trials for this review (see Figure 1 for the study flow details).

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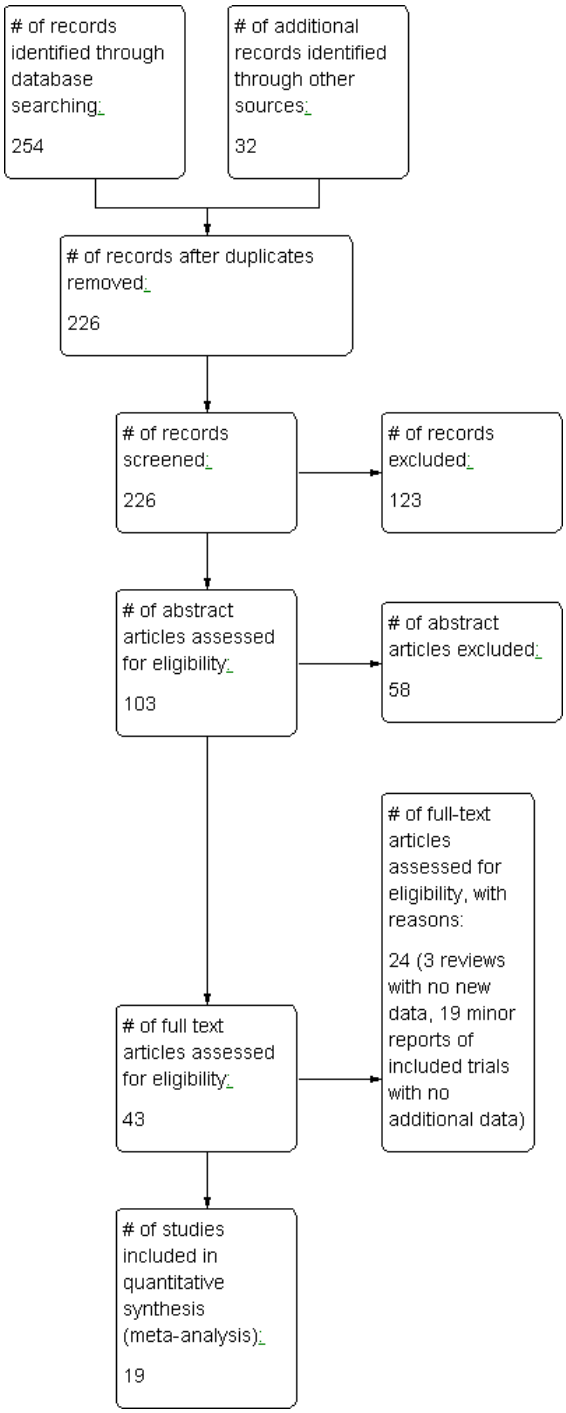
Figure 1. Study flow diagram.



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Included studies

The included trials were published between 1967 and 1999, and the review authors are unaware of any ongoing RCTs in the area. The trials 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 trial (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 at 3 ATA for between 30 and 40 minutes. The exception was Haffty 1999 who used oxygen at 4 ATA and required all patients to be anaesthetised and intubated because of the risk of oxygen toxic seizures. However, the total number of treatment sessions varied widely. The shortest fractionation scheme was two sessions only, separated by three weeks (Haffty 1999) and the longest was 40 sessions over eight weeks (Cade 1967; Cade 1978). 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 intracavity 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 QoL.

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).

Risk of bias in included studies

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 we were able to pool relatively few analyses, we did not use study quality 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 was quasi-random in two studies: Shigematsu 1973 employed 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 Characteristics of included studies, but were generally reasonably consistent across trials.

Blinding

None of the studies included were blinded in any way.

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Intention-to-treat (ITT) 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. We have performed sensitivity analysis using best and worse case scenarios, where possible, for dichotomous outcomes involving those studies with losses to follow-up.

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

Effects of interventions

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 (lgHR).

One year mortality

Mortality at one year with head and neck cancer (Analysis 1.1)

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), for 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 HBOT (RR of death with HBOT was 0.83; 95% CI 0.70 to 0.98, P = 0.03). There was no evidence of substantial heterogeneity between trials overall (I^2 = 0%), but some heterogeneity for the trials using fewer than 12 sessions of HBO compared to more than 12 using air (I^2 = 39%), so these results are achieved using a random effects model. There is an absolute risk reduction of 9.2% when using HBOT (number needed to treat (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 (Analysis 1.2); worst case scenario: RR 0.93; 95% CI 0.76 to 1.15, P = 0.51 (Analysis 1.3). However, the risk for those receiving 12 fractions with HBO versus more than 12 fractions in air is not sensitive to allocation of withdrawals (worst case scenario: RR 0.72; 95% CI 0.56 to 0.92, P = 0.01).

Mortality at one year with cancer of the uterine cervix (Analysis 1.4)

Four trials reported this outcome (Dische 1999; Tobin 1971; Ward 1979; Watson 1978), for 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 HBOT (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 (I^2 = 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 (Analysis 1.5); worst case scenario: RR 0.91; 95% CI 0.72 to 1.15, P = 0.43 (Analysis 1.6)).

Mortality at one year with cancer of the urinary bladder (Analysis 1.7)

Four trials reported this outcome (Cade 1967; Cade 1978; Plenk 1972; Van Den Brenk 1968), for 330 subjects after exclusion of withdrawals (14% of the total subjects in this review), with 165 allocated to both HBOT and control. There was no statistically significant reduction in the proportion of subjects dying within one year after receiving radiation therapy with HBOT (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 (I^2 = 39%) (fixed-effect 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 (Analysis 1.8); worst case scenario: RR 1.03; 95% CI 0.78 to 1.34, P = 0.86 (Analysis 1.9)).

Mortality at one year with carcinoma of the bronchus (Analysis 1.10)

One trial reported this outcome (Cade 1967), involving 49 subjects after exclusion of withdrawals (2% of the total subjects in this review), with 25 (51%) allocated to HBOT and 24 (49%) to control. There was no statistically significant difference in the

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proportion of subjects dying within one year after receiving radiation therapy with HBOT (RR 1.09; 95% CI 0.72 to 1.64, P = 0.69).

Mortality at one year with carcinoma of the rectum (Analysis 1.11)

One trial reported this outcome (Tobin 1971), involving four subjects (0.2% of the total subjects in this review), with two allocated to both HBOT and control. Both subjects died following HBOT and one of those receiving the control. There was no statistically significant difference in the proportion of subjects dying within one year after receiving radiation therapy with HBOT (RR 1.67; 95% CI 0.48 to 5.76, P = 0.42).

Mortality at one year with carcinoma of the oesophagus (Analysis 1.12)

One trial reported this outcome (Tobin 1971), involving four subjects (0.2% of the total subjects in this review), with two allocated to both HBOT and control. One subject died following HBOT and both of those receiving the control. There was no statistically significant difference in the proportion of subjects dying within one year after receiving radiation therapy with HBOT (RR 0.2; 95% CI 0.00 to 8.82, P = 0.4).

Mortality at one year with glioblastoma (Analysis 1.13)

One trial reported this outcome (Tobin 1971), involving four subjects (0.2% of the total subjects in this review), with two allocated to both HBOT and control. All subjects died within one year, making analysis unhelpful.

Mortality at two years

Mortality at two years with head and neck cancer (Analysis 2.1)

Three trials reported this outcome (Haffty 1999; Sealy 1986; Tobin 1971) for 189 subjects after exclusion of withdrawals (8% of the total subjects in this review), with 92 (49%) allocated to HBOT 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 HBOT (RR 0.84; 95% CI 08.3 to 1.12, P = 0.64), neither did subgroup analysis suggest any benefit with different fractionation schemes. There was no evidence of substantial heterogeneity between trials overall (I^2 = 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 (Analysis 2.2); worst case scenario: RR 1.00; 95% CI 0.86 to 1.15, P = 0.97 (Analysis 2.3)).

Mortality at two years with cancer of the uterine cervix (Analysis 2.4)

Four trials reported this outcome (Fletcher 1977; Glassburn 1974; Tobin 1971; Watson 1978) for 607 subjects after exclusion of withdrawals (27% of the total subjects in this review), with 294 (48%) allocated to HBOT 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 HBOT (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 (I^2 = 36%) (random-effects model). No trials had suffered any losses to follow-up after randomisation.

Mortality at two years with urinary bladder carcinoma (Analysis 2.5 comparison 2, outcomes 05, 06, 07)

Two trials reported this outcome (Plenk 1972; Tobin 1971) for 24 subjects after exclusion of withdrawals (1% of the total subjects in this review), with 12 allocated to both HBOT 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 HBOT (RR 1.57; 95% CI 0.63 to 3.92, P = 0.33). There was no evidence of substantial heterogeneity between trials overall (I^2 = 0%) (fixed-effect model). The risk of death with HBOT 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 (Analysis 2.6); worst case scenario: RR 5.18; 95% CI 2.18 to 12.31, P = 0.0002 (Analysis 2.7)).

Mortality at five years

Mortality at five years with head and neck cancer (Analysis 3.1)

Six trials reported this outcome (Berry 1979; Chang 1973; Haffty 1999; Henk 1977a; Henk 1986; Sause 1979) for 550 subjects after exclusion of withdrawals (24% of the total subjects in this review), with 258 (47%) allocated to HBOT and 292 (53%) to control. Over all fractionation schemes there was a statistically significant reduction in the proportion of subjects dying within

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five years after receiving radiation therapy with HBOT (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 (I^2 = 37%), however little evidence for heterogeneity within each subgroup of fraction schemes(fixed-effect 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 (Analysis 3.2); worst case scenario: RR 0.96; 95% CI 0.81 to 1.13, P = 0.6 (Analysis 3.3)), however, the risk for those receiving 12 fractions with HBO versus more than 12 fractions in air is not sensitive to allocation of withdrawals (worst case scenario: RR 0.75; 95% CI 0.59 to 0.96, P = 0.02).

Mortality at five years with cancer of the uterine cervix (Analysis 3.4))

Four trials reported this outcome (Brady 1981; Dische 1999; Ward 1979; Watson 1978) for 772 subjects after exclusion of withdrawals (34% of the total subjects in this review), with 367 (48%) allocated to HBOT and 405 (52%) to control. There was no significant reduction in the proportion of subjects dying within five years after receiving radiation therapy with HBOT (RR 0.95; 95% CI 0.80 to 1.14, P = 0.59). There was considerable heterogeneity between trials (I^2 = 63%) for which Watson 1978 is largely responsible (suggesting a strong beneficial effect of HBOT) (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 (Analysis 3.5); worst case scenario: RR 0.98, 95% CI 0.81 to 1.18, P = 0.8 (Analysis 3.6)).

Mortality at five years with urinary bladder cancer (Analysis 3.7))

One trial reported this outcome (Cade 1978) for 236 subjects after exclusion of withdrawals (10% of the total subjects in this review), with 118 allocated to each of HBOT and control. There was no reduction in the proportion of subjects dying within five years after receiving radiation therapy with HBOT (RR 1.04; 95% CI 0.88 to 1.22, P = 0.67). We could not perform a sensitivity analysis for the five subjects lost to analysis due to lack of information about original allocation.

2. Failure to control local tumour

Failure to control local tumour at three months in head and neck cancer (Analysis 4.1))

Four trials reported this outcome (Haffty 1999; Henk 1977a; Shigematsu 1973; Van Den Brenk 1968) for 446 subjects after exclusion of withdrawals (20% of the total subjects in this review), with 212 (48%) allocated to HBOT 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 HBOT (RR of failure with HBOT 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 (I^2 = 26%) (fixed-effect 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 (Analysis 4.2); worst case scenario: RR 0.59; 95% CI 0.35 to 1.00, P = 0.05 (Analysis 4.3)).

3. Local recurrence

Local recurrence at one year

Local recurrence at one year with head and neck cancer (Analysis 5.1)

Five trials reported this outcome (Haffty 1999; Henk 1977a; Henk 1986; Sealy 1986; Shigematsu 1973) for 714 subjects after exclusion of withdrawals (31% of the total subjects in this review), with 338 (47%) allocated to HBOT 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 HBOT (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 HBOT versus more than 12 with control 0.73; 95% CI 0.56 to 0.94, P = 0.01). There was no evidence of heterogeneity between trials overall (I^2 = 0%) (fixed-effect model). There is an absolute risk reduction of 21.1% when using HBOT (NNT to avoid one recurrence = 5; 95% CI

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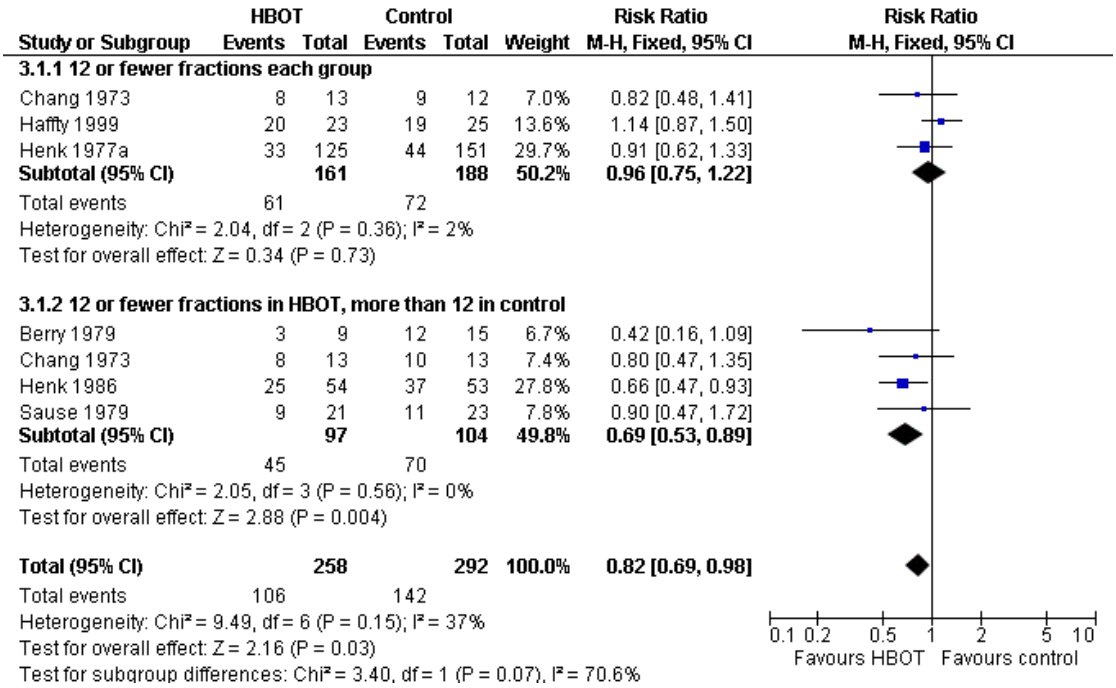
4 to 8). The overall reduction in failure to control tumour is not sensitive to the allocation of withdrawals (best case scenario: RR 0.61; 95% CI 0.51 to 0.71, P < 0.00001 (Analysis 5.2); worst case scenario: RR 0.75; 95% CI 0.65 to 0.87, P = 0.0002 (Analysis 5.3)). Figure 2

Figure 2. Forest plot of comparison: Death at five years for head and neck cancer: outcome 3.1



Local recurrence at one year with cancer of the uterine cervix (Analysis 5.4)

Three trials reported this outcome (Dische 1999; Ward 1979; Watson 1978) for 714 subjects after exclusion of withdrawals (31% of the total subjects in this review), with 338 (47%) allocated to HBOT 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 HBOT (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 (I^2 = 23%), but significant heterogeneity when comparing groups who had received fewer than 12 fractions (I^2 = 37%) (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 (Analysis 5.5); worst case scenario: RR 0.87; 95% CI 0.63 to 1.19, P = 0.38 (Analysis 5.6)).

Local recurrence at two years

Local recurrence at two years with head and neck cancer (Analysis 6.1)

One trial reported this outcome (Haffty 1999) for 48 subjects (2% of the total subjects in this review), with 23 (48%) allocated to HBOT and 25 (52%) to control. There was no significant reduction in the incidence of local tumour recurrence following radiation therapy with HBOT (RR 0.83; 95% CI 0.60 to 1.14, P = 0.25).

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Local recurrence at two years with cancer of the uterine cervix (Analysis 6.2)

Two trials reported this outcome (Glassburn 1974; Watson 1978) for 360 subjects after exclusion of withdrawals (16% of the total subjects in this review), with 178 (49%) allocated to HBOT 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 HBOT (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 (I^2 = 67%) (random-effects model). Overall, there is a risk reduction of 23% when using HBOT (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

Local recurrence at five years with head and neck cancer (Analysis 7.1)

Five trials reported this outcome (Berry 1979; Haffty 1999; Henk 1977a; Henk 1986; Sause 1979) for 495 subjects after exclusion of withdrawals (22% of the total subjects in this review), with 229 (46%) allocated to HBOT 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 HBOT (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 (I^2 = 32%), and substantial heterogeneity for those trials comparing fewer than 12 fractions in HBOT with 12 or more fractions in control (I^2 = 63%) (random-effects model). Overall, there is an absolute risk reduction of 19% when using HBOT (NNT to avoid one recurrence = 6; 95% CI 4 to 11), and the absolute risk reduction 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 (Analysis 7.2); worst case scenario: RR 0.84; 95% CI 0.66 to 1.06, P = 0.14 (Analysis 7.3)).

Local recurrence at five years with cancer of the uterine cervix (Analysis 7.4)

Four trials reported this outcome (Brady 1981; Dische 1999; Ward 1979; Watson 1978) for 772 subjects (34% of the total subjects in this review), with 367 (48%) allocated to HBOT 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 (I^2 = 68%) (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 (Analysis 7.5); worst case scenario: RR 0.89; 95% CI 0.76 to 1.03, P = 0.11 (Analysis 7.6)).

4. Development of metastasis

Metastases at one year

Metastases at one year with cancer of the uterine cervix (Analysis 8.1)

One trial reported this outcome (Watson 1978) for 320 subjects (23% of the total subjects in this review), with 161 (50.3%) allocated to HBOT and 159 (49.7%) to control. There were no withdrawals or losses to follow-up. There was no significant reduction in the incidence of metastases following radiation therapy with HBOT (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

Metastases at two years with cancer of the uterine cervix (Analysis 9.1)

Three trials reported this outcome (Fletcher 1977; Glassburn 1974; Watson 1978) for 522 subjects (23% of the total subjects in this review), with 251 (48%) allocated to HBOT and 271 (52%) to control. There were no withdrawals or losses to follow-up. There was no significant reduction in the incidence of metastases following radiation therapy with HBOT (RR 1.05; 0.84 to 1.31, P = 0.70).

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Metastases at two years with cancer of the urinary bladder (Analysis 9.2)

Two trials reported this outcome (Cade 1967; Plenk 1972) for 80 subjects (2% of the total subjects in this review), with 25 (51%) allocated to HBOT 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 follow-up. There was no significant difference in the incidence of metastases following radiation therapy with HBOT (RR 2.00; 95% CI 0.58 to 6.91, P = 0.27).

Metastases at two years with cancer of the bronchus (Analysis 9.3)

One trial reported this outcome (Cade 1967) for 49 subjects (3.5% of the total subjects in this review), with 39 (51%) allocated to HBOT and 41 (49%) to control. There were no withdrawals or losses to follow-up. There was no significant difference in the incidence of metastases following radiation therapy with HBOT (RR 1.04; 95% CI 0.60 to 1.80, P = 0.89).

Metastases at five years

Metastases at five years with cancer of the head and neck (Analysis 10.1)

One trial reported this outcome (Chang 1973) for 50 subjects (2% of the total subjects in this review), with 26 (52%) allocated to HBOT and 24 (48%) to control. There were no withdrawals or losses to follow-up. There was no significant reduction in the incidence of metastases following radiation therapy with HBOT (RR 0.46; 95% CI 0.09 to 2.30, P = 0.34).

Metastases at five years with cancer of the uterine cervix (Analysis 10.2)

Three trials reported this outcome (Brady 1981; Ward 1979; Watson 1978) for 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 HBOT (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 HBOT 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 (I^2 = 58%) (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 (Analysis 10.3); worst case scenario: RR 0.85; 95% CI 0.56 to 1.31, P = 0.46 (Analysis 10.4)).

5. Adverse effects

Death from radiation tissue effects (Analysis 11.1)

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

Severe radiation tissue injury (Analysis 11.2)

Seven trials reported this outcome (Brady 1981; Haffty 1999; Henk 1986; Sause 1979; Sealy 1986; Watson 1978; Ward 1979) for 779 subjects after exclusion of withdrawals (34% of the total subjects in this review), with 379 (48%) allocated to HBOT and 400 (52%) to control. There was a statistically significant increase in the chance of severe radiation tissue injury following HBOT (RR 2.35; 95% CI 1.66 to 3.33, P < 0.00001). There was little heterogeneity between trials overall (I^2 = 15%) (fixed-effect model). There is an absolute risk increase of 12% when using HBOT (number needed to harm (NNH) to cause one severe injury = 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 (Analysis 11.3); worst case scenario: RR 2.69; 95% CI 1.92 to 3.77, P < 0.00001 (Analysis 11.4)).

Acute central nervous system toxicity (Analysis 11.5)

Four trials reported this outcome (Cade 1967; Chang 1973; Plenk 1972; Sealy 1986) for 331 subjects after exclusion of withdrawals (15% of the total subjects in this review), with 150 (45%) allocated to HBOT and 181 (55%) to control. There was a statistically significant increase in the chance of severe radiation tissue injury following HBOT (RR 6.76; 95% CI 1.16 to 39.31, P = 0.03). There was no evidence of important heterogeneity between trials overall (I^2 = 0%) (fixed-effect model). There is an absolute risk

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increase of 5% when using HBOT (NNH to cause one episode = 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 (Analysis 11.6); worst case scenario: RR 9.74; 95% CI 1.73 to 54.98, P = 0.01 (Analysis 11.7)).

Middle ear barotrauma (Analysis 11.8))

Only one trial reported this outcome (Cade 1967) for 89 subjects (4% of the total subjects in this review), with 45 allocated to HBOT 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 HBOT (RR 6.85; 95% CI 0.36 to 128.83, P = 0.20).

DISCUSSION

Summary of main results

We were able to pool data for a number of clinical outcomes of interest, however interpretation of some results was complicated by consideration of the 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 HBOT 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 HBO (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 HBOT (RR at one year 0.93, P = 0.53; RR at five years 0.96; 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 HBOT 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 significantly 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).

Overall completeness and applicability of evidence

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.

We 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. We did not locate further trials when we repeated the searches in September 2008 and March 2011. Ten trials included subjects with head and neck cancers, seven trials of carcinoma of the uterine cervix, five trials of carcinoma of the urinary bladder and one trial each with carcinoma of the bronchus, glioblastoma, cancer of the oesophagus and cancer of the rectum. We found some evidence that radiotherapy with HBO reduces the one and five year mortality rate 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 HBOT, particularly the incidence of oxygen toxic seizures and the chance of suffering severe radiation injury. There were no reliable data from these trials to confirm any beneficial effect of HBOT for other malignancies studied, nor on the incidence of metastatic disease for cancers of any primary site.

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, we were only able to conduct a subgroup analysis for the different fractionation schemes employed. Specifically, there were no children included and no trials used a sequential approach to HBOT and radiation therapy, while the dose of oxygen administered was remarkably uniform per session.

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Quality of the evidence

Although study quality varied across these trials, in general the methodology was reasonable as 13 of the 19 included trials employed a reliable method of randomisation and allocation concealment. Although none of the trials employed a sham therapy, most of our clinical outcomes, such as mortality and cancer recurrence, were unlikely to be subject to participant or observer bias. Some major problems for this review were the poor reporting of methodological quality in some of these trials, variability in entry criteria, the nature and timing of outcomes, and poor reporting of outcomes. 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 lgHR. None of the trials blinded participants, investigators or outcome assessors to treatment.

Potential biases in the review process

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.

Agreements and disagreements with other studies or reviews

Our findings are in general agreement with previously published reviews of the area. In his review of modifying agents designed to sensitise tumours to the effect of radiotherapy, Overgaard has suggested that HBOT was abandoned before a measured evaluation was made of the true clinical impact (Overgaard 1996). This decision seems to have been based more on convenience and logistics rather than a demonstrated superiority of alternative sensitising agents.

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence that HBOT 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. HBOT 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 HBOT 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; and
- the cost-utility of the therapy.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

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 3 ATA 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	

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 group
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 3 ATA breathing 100% oxygen, total compression time about 40 minutes

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Brady 1981 (*Continued*)

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

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 3 ATA 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

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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 65 participants: 6000 rads in 40 fractions over 8 weeks ○ 1B. Portsmouth 57 participants: 3600 rads in 6 fractions over 2.5 weeks ○ 2. Oxford 25 participants: 4250 rads in 10 fractions over 4.5 weeks ○ 3.Glasgow 27 participants: 4500 rads in 24 fractions over 7 weeks ○ 4A. Mount Vernon 41 participants: 6000 rads in 30 fractions over 6 weeks ○ 4B. Mount Vernon 26 participants: 4725 rads in 15 fractions over 4.5 weeks • HBOT: same regimen, with all external beam radiotherapy conducted while breathing 100% oxygen at 3 ATA 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

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 ○ 6000 rads in 30 fractions over 6 weeks ○ 4200 rads in 7 fractions over 3.5 weeks • HBOT: 3600 rads in 6 fractions over 3 weeks while breathing 100% oxygen at 3 ATA for approximately 30 minutes

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Chang 1973 (*Continued*)

Outcomes	Death at 1 and 5 years, early local tumour control, metastatic disease at 5 years, oxygen toxicity. HBOT group results split between the two controls for analysis	
Notes	Schulz rating: randomisation: A; allocation concealment: B; selection bias: A; blinding: C	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

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: ○ 88 participants: 4500 rads in 10 fractions over 5 weeks ○ 82 participants: 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 3 ATA breathing oxygen for approximately 30 minutes	
Outcomes	Death 1 and 5 years, locoregional control 1 and 5 years, death by late radiation effects at 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	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

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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 3 ATA breathing 100% oxygen, total compression time about 40 minutes
Outcomes	Death at 2 years, metastatic disease at 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

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 participants displayed high rate of gastrointestinal complications. All external beam radiotherapy conducted at 3 ATA breathing 100% oxygen, total compression time about 40 minutes
Outcomes	Death at 27 months, local tumour recurrence at 27 months, metastases at 27 months
Notes	An interim report that does not seem to have been reported in a complete paper to date. Also see Faust 1969 Schulz rating: randomisation: C; allocation concealment: B; selection bias: A; blinding: C

Risk of bias

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Glassburn 1974 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

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 4 ATA 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

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 3 ATA 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 at 1 to 5 years, significant radiation tissue effects at 6 months
Notes	Other reports of this trial in Henk 1974, Henk 1975, Kunkler 1968 Schulz rating: randomisation: C; allocation concealment: B; selection bias: B; blinding: C

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Henk 1977a (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Henk 1986

Methods	RCT stratified by site of tumour (mouth, oropharynx, nasal sinus, nasopharynx, larynx, hypopharynx and middle ear). Allocation concealment 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 3 ATA 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 1977 Schulz rating: randomisation: A; allocation concealment: A; selection bias: A; blinding: C

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

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 fractions over six weeks • HBOT: 4800 rads in 12 fractions over about four weeks at 3 ATA breathing oxygen for about 40 minutes
Outcomes	Death at one and two years, oxygen toxicity

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Plenk 1972 (*Continued*)

Notes	Schulz rating: randomisation: A; allocation concealment: B; selection bias: C; blinding: C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Sause 1979

Methods	RCT of previously untreated head 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 3 ATA for about 30 minutes
Outcomes	Death at 2 to 8 years, local tumour control and late radiation tissue injury
Notes	5 participants excluded from analysis because they died from 'intercurrent disease' prior to 2 year follow-up Schulz rating: randomisation: C; allocation concealment: B; selection bias: B; blinding: C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

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 3 ATA for 30 to 40 minutes total

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Sealy 1986 (*Continued*)

	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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

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 dropouts 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 3 ATA 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

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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 carcinoma 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 3 ATA 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Van Den Brenk 1968

Methods	Pseudo-RCT 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

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Van Den Brenk 1968 (*Continued*)

	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. 2900 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	C - Inadequate

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 3 ATA 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Ward 1979 (*Continued*)

Allocation concealment (selection bias)	Low risk	A - Adequate

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: (all but group 1. had radium insertion) ○ 1. Portsmouth 37 participants: 3600 rads over 6 or 7 fractions in 3 weeks ○ 2. Oxford 34 participants: 4250 rads in 10 fractions in 4.5 weeks ○ 3. Glasgow 162 participants: 4500 rads in 20 fractions over 4 weeks ○ 4. Mount Vernon 87 participants: 5500 rads in 27 fractions over 6 weeks • 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

ATA - atmospheres absolute
HBOT - hyperbaric oxygen therapy
RCT - randomised controlled trial
Rads -
SCC - squamous cell carcinoma

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Characteristics of excluded studies *[ordered by study ID]*

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
Mayer 2005	Review, no new data
McEwen 1968	More fully reported in Cade 1967
McEwen 1972	More fully reported in Cade 1967
MRCWP 1978	Summary of trials with no new data
Overgaard 2007	Review, no new data
Sealy 1978	More fully reported in Sealy 1986
Ward 1973	More fully reported in Ward 1979
Ward 1974	More fully reported in Ward 1979

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(*Continued*)

Ward 1978	More fully reported in Ward 1979
Wiernik 1973	More fully reported in Watson 1978 and Cade 1978

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DATA AND ANALYSES

Comparison 1. Death at one year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck cancer	9	710	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
1.1 12 or fewer fractions each group	5	412	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.17]
1.2 12 or fewer fractions with HBOT, more than 12 with control	4	281	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.41, 1.08]
1.3 More than 12 fractions each group	1	17	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.13, 2.70]
2 Head and neck - best case scenario	9	743	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.62, 0.85]
2.1 12 or fewer fractions each group	5	439	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.64, 1.02]
2.2 12 or fewer fractions with HBOT, more than 12 with control	4	287	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.43, 0.91]
2.3 More than 12 fractions each group	1	17	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.13, 2.70]
3 Head and neck - worst case scenario	9	743	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.76, 1.15]
3.1 12 or fewer fractions each group	5	439	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.90, 1.36]
3.2 12 or fewer fractions with HBOT, more than 12 with control	4	287	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.45, 1.13]
3.3 More than 12 fractions each group	1	17	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.13, 2.70]
4 Uterine cervix cancer	4	728	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.11]
4.1 12 or fewer fractions each groups	3	329	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.70, 1.38]
4.2 More than 12 fractions each group	3	399	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.10]
5 Uterine cervix - best case scenario	4	732	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.69, 1.10]
6 Uterine cervix - worst case scenario	4	732	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.15]
7 Urinary bladder cancer	4	330	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.74, 1.27]
7.1 12 or fewer fractions each group	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.35]
7.2 12 or fewer fractions with HBOT, more than 12 with control	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.44, 1.51]
7.3 More than 12 fractions each group	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.68, 3.00]

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7.4 Mixed fractionation scheme	1	236	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.73, 1.44]
8 Urinary bladder - best case scenario	4	337	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.71, 1.21]
9 Urinary bladder - worst case scenario	4	337	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.78, 1.34]
10 Bronchial cancer	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.72, 1.64]
11 Rectal cancer	1	4	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.48, 5.76]
12 Oesophageal cancer	1	4	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.17, 2.07]
13 Gliobastoma	1	4	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.49, 2.05]

Comparison 2. Death at two years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck cancer	3	189	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.12]
1.1 12 or fewer fractions in each group	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.76, 1.40]
1.2 12 or fewer fractions with HBOT, more than 12 with control	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.09]
1.3 More than 12 fractions in both HBOT and control	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.37, 3.76]
2 Head and neck - best case scenario	3	195	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.79, 1.07]
2.1 12 or fewer fractions in each group	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.76, 1.40]
2.2 12 or fewer fractions with HBOT, more than 12 with control	1	130	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.73, 1.03]
2.3 More than 12 fractions in both HBOT and control	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.37, 3.76]
3 Head and neck - worst case scenario	3	195	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.15]
3.1 12 or fewer fractions in each group	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.76, 1.40]
3.2 12 or fewer fractions with HBOT, more than 12 with control	1	130	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.14]
3.3 More than 12 fractions in both HBOT and control	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.37, 3.76]
4 Uterine cervix cancer	4	607	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.76, 1.15]
4.1 12 or fewer fractions in HBOT and control	1	71	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.47, 1.09]
4.2 More than 12 fractions in HBOT and control	4	536	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.81, 1.21]
5 Urinary bladder carcinoma	2	24	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.63, 3.92]
6 Urinary bladder - best case	2	58	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.04, 5.24]

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7 Urinary bladder - worst case	2	58	Risk Ratio (M-H, Fixed, 95% CI)	5.18 [2.18, 12.31]

Comparison 3. Death at five years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck cancer	6	550	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.69, 0.98]
1.1 12 or fewer fractions each group	3	349	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.75, 1.22]
1.2 12 or fewer fractions in HBOT, more than 12 in control	4	201	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.53, 0.89]
2 Head and neck - best case scenario	6	575	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.64, 0.92]
2.1 12 or fewer fractions in each group	3	368	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.12]
2.2 12 or fewer fractions in HBOT, more than 12 in control	4	207	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.51, 0.85]
3 Head and neck - worst case scenario	6	575	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.81, 1.13]
3.1 12 or fewer fractions each group	3	368	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.92, 1.45]
3.2 12 or fewer fractions in HBOT, more than 12 in control	4	207	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.59, 0.96]
4 Uterine cervix cancer	4	772	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.14]
4.1 12 or fewer fractions each group	3	329	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.62, 1.34]
4.2 More than 12 fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.15]
4.3 12 or fewer fractions in HBOT versus more than 12 in control	1	58	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.70, 1.61]
5 Uterine cancer - best case scenario	4	783	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.09]
5.1 12 or fewer fractions in each group	3	333	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.61, 1.28]
5.2 More than 12 fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.15]
5.3 12 or fewer fractions in HBOT versus more than 12 in control	1	65	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.57, 1.32]
6 Uterine cancer - worst case scenario	4	783	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.81, 1.18]
6.1 12 or fewer fractions in each group	3	333	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.63, 1.38]

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6.2 More than 12 fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.15]
6.3 12 or fewer fractions in HBOT versus more than 12 in control	1	65	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.79, 1.77]
7 Urinary bladder cancer	1	236	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.88, 1.22]

Comparison 4. Failure to control local tumour at three months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck cancer	5	446	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.39, 0.85]
1.1 12 or fewer fractions each group	5	420	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.34, 0.88]
1.2 Less than 12 fractions in HBOT group versus more than 12 in control	1	26	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.24, 1.82]
2 Head and neck cancer - best case scenario	5	465	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.41, 0.78]
2.1 12 or fewer fractions in each group	5	439	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.36, 0.80]
2.2 Less than 12 fractions in HBOT versus more than 12 in control	1	26	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.24, 1.82]
3 Head and neck - worst case scenario	5	465	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.35, 1.00]
3.1 12 or fewer fractions in each group	5	439	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.30, 1.05]
3.2 Less than 12 fractions in HBOT versus more than 12 in control	1	26	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.24, 1.82]

Comparison 5. Local recurrence at one year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck cancer	5	582	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.56, 0.78]
1.1 12 or fewer fractions each group	3	355	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.50, 0.77]
1.2 12 or fewer fractions with HBOT, more than 12 with control	2	227	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.94]
2 Head and neck cancer - best case scenario	5	611	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.51, 0.71]

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2.1 12 or fewer fractions in each group	3	374	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.45, 0.70]
2.2 12 or fewer fractions with HBOT, more than 12 with control	2	237	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.53, 0.87]
3 Head and neck cancer - worst case scenario	5	611	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.65, 0.87]
3.1 12 or fewer fractions in each group	3	374	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.60, 0.87]
3.2 12 or fewer fractions with HBOT, more than 12 with control	2	237	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.64, 1.03]
4 Uterine cervix cancer	3	714	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.63, 1.06]
4.1 12 or fewer fractions each group	3	329	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.57, 1.27]
4.2 more than 12 fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.28]
5 Uterine cervix cancer - best case scenario	3	718	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.63, 1.02]
5.1 12 or fewer fractions in each group	3	333	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.58, 1.17]
5.2 More than 12 fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.28]
6 Uterine cervix cancer - worst case scenario	3	718	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.63, 1.19]
6.1 12 or fewer fractions in each group	3	333	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.56, 1.58]
6.2 More than 12 fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.28]

Comparison 6. Local recurrence at two years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck cancer	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.60, 1.14]
2 Uterine cervix cancer	2	360	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.38, 0.97]
2.1 12 or fewer fractions in each group	1	71	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.37, 0.77]
2.2 More than 12 fractions in each group	2	289	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.26, 1.73]

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Comparison 7. Local recurrence at five years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck cancer	5	495	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.62, 0.95]
1.1 12 or fewer fractions in each group	2	324	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.88]
1.2 12 or fewer fractions in HBOT, more than 12 in control	3	171	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.39, 1.43]
2 Head and neck cancer - best case scenario	5	521	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.57, 0.86]
2.1 12 or fewer fractions in each group	2	343	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.52, 0.94]
2.2 12 or fewer fractions in HBOT, more than 12 in control	3	178	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.43, 1.12]
3 Head and neck cancer - worst case scenario	5	521	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.66, 1.06]
3.1 12 or fewer fractions in each group	2	343	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.69, 0.95]
3.2 12 or fewer fractions in HBOT, more than 12 in control	3	178	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.38, 1.71]
4 Uterine cervix cancer	4	772	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.65, 1.13]
4.1 12 or fewer fractions each group	3	329	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.49, 1.41]
4.2 12 or fewer fractions in HBOT group versus more than 12 fractions in control	1	58	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.58, 2.71]
4.3 12 or more fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.32]
5 Uterine cervix cancer - best case scenario	4	783	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.97]
5.1 12 or fewer fractions in each group	3	333	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.70, 1.05]
5.2 12 or fewer fractions in HBOT, more than 12 in controls	2	385	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 1.01]
5.3 More than 12 fractions in each group	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.44, 1.89]
6 Uterine cervix cancer - worst case scenario	4	783	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.76, 1.03]
6.1 12 or fewer fractions in each group	3	333	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.10]
6.2 12 or fewer fractions in HBOT, more than 12 in controls	2	385	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 1.01]

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6.3 More than 12 fractions in each group	1	65	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.78, 3.28]

Comparison 8. Metastases at one year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Uterine cervix cancer	1	320	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.52, 1.19]
1.1 10 or fewer fractions	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.35, 2.73]
1.2 11 or more fractions	1	249	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.48, 1.19]

Comparison 9. Metastases at two years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Uterine cervix cancer	3	522	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.84, 1.31]
1.1 More than 12 fractions in each group	3	522	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.84, 1.31]
2 Urinary bladder carcinoma	2	80	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.58, 6.91]
3 Carcinoma of the bronchus	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.60, 1.80]

Comparison 10. Metastases at five years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck carcinoma	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.09, 2.30]
2 Uterine cervix cancer	3	456	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.50, 1.26]
2.1 12 or fewer fractions each group	2	149	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.45, 0.99]
2.2 12 or fewer fractions in HBOT group versus more than 12 fractions in control	1	58	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.12]
2.3 More than 12 fractions in each group	1	249	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.78, 1.26]
3 Uterine cervix cancer - best case scenario	3	467	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.46, 1.26]
3.1 12 or fewer fractions in each group	2	153	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.45, 0.98]
3.2 12 or fewer fractions in HBOT versus more than 12 in control	1	65	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.79]

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3.3 More than 12 fractions in each group	1	249	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.78, 1.26]
4 Uterine cervix cancer - worst case scenario	3	467	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.56, 1.31]
4.1 12 or fewer fractions in each group	2	153	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.35, 2.68]
4.2 12 or fewer fractions in HBOT versus more than 12 in control	1	65	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.11, 1.38]
4.3 More than 12 fractions in each group	1	249	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.78, 1.26]

Comparison 11. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death through radiation tissue injury	2	633	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.89, 3.03]
2 Severe radiation tissue injury	7	779	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.66, 3.33]
3 Severe radiation tissue injury - best case scenario	7	803	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.39, 2.69]
4 Severe radiation tissue injury - worst case scenario	7	803	Risk Ratio (M-H, Fixed, 95% CI)	2.69 [1.92, 3.77]
5 Acute central nervous system oxygen toxicity	4	331	Risk Ratio (M-H, Fixed, 95% CI)	6.76 [1.16, 39.31]
5.1 12 or fewer oxygen fractions	3	242	Risk Ratio (M-H, Fixed, 95% CI)	4.30 [0.47, 39.60]
5.2 More than 12 oxygen fractions	1	89	Risk Ratio (M-H, Fixed, 95% CI)	10.76 [0.61, 188.98]
6 Acute central nervous system toxicity - best case scenario	4	337	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.81, 11.10]
6.1 12 or fewer oxygen fractions	3	248	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.26, 6.53]
6.2 More than 12 oxygen fractions	1	89	Risk Ratio (M-H, Fixed, 95% CI)	10.76 [0.61, 188.98]
7 Acute central nervous system toxicity - worst case scenario	4	337	Risk Ratio (M-H, Fixed, 95% CI)	9.74 [1.73, 54.98]
7.1 12 or fewer oxygen fractions	3	248	Risk Ratio (M-H, Fixed, 95% CI)	9.12 [1.05, 79.50]
7.2 More than 12 oxygen fractions	1	89	Risk Ratio (M-H, Fixed, 95% CI)	10.76 [0.61, 188.98]
8 Middle ear barotrauma	1	89	Risk Ratio (M-H, Fixed, 95% CI)	6.85 [0.36, 128.83]

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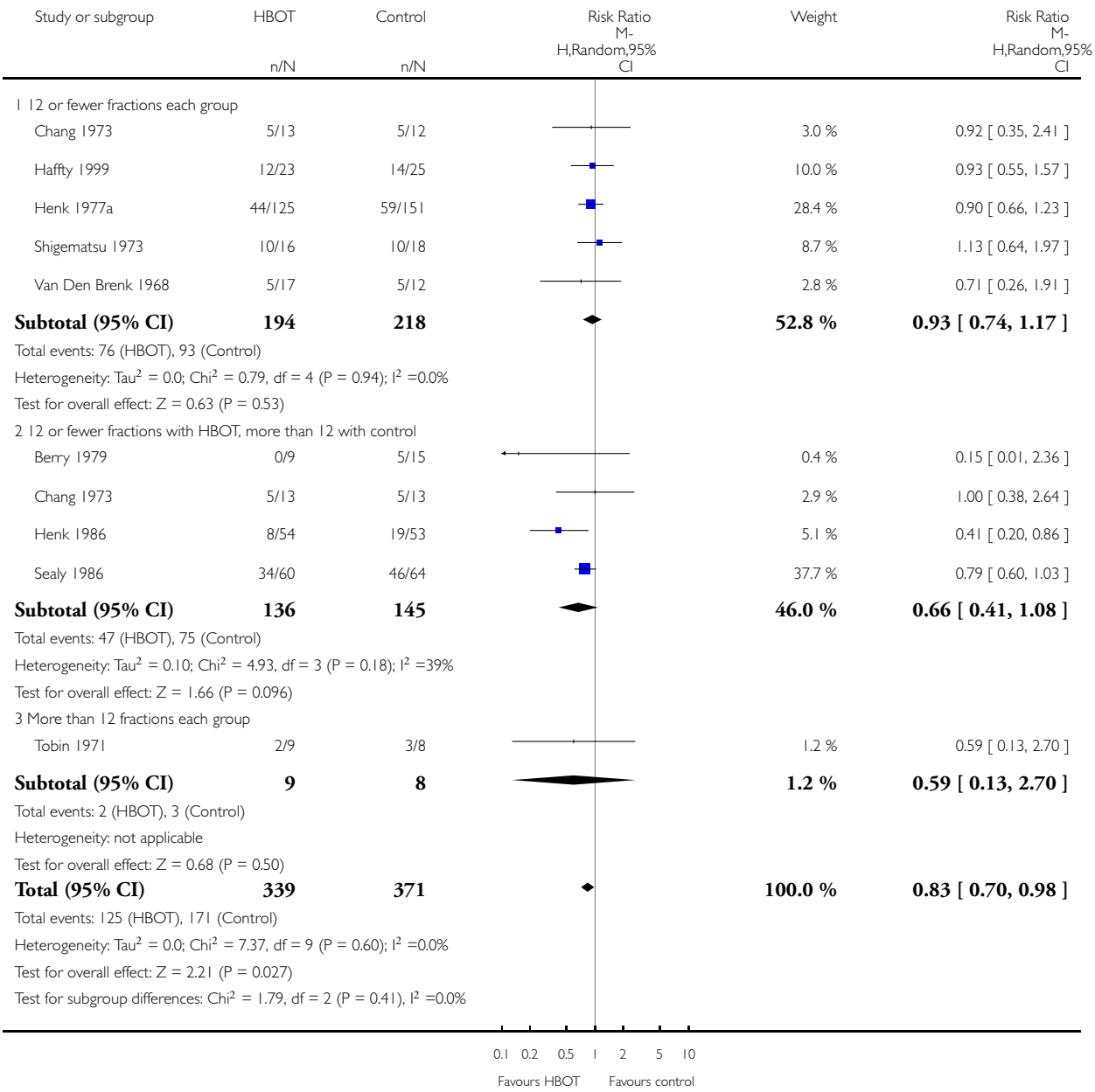
Analysis 1.1. Comparison 1 Death at one year, Outcome 1 Head and neck cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 1 Head and neck cancer



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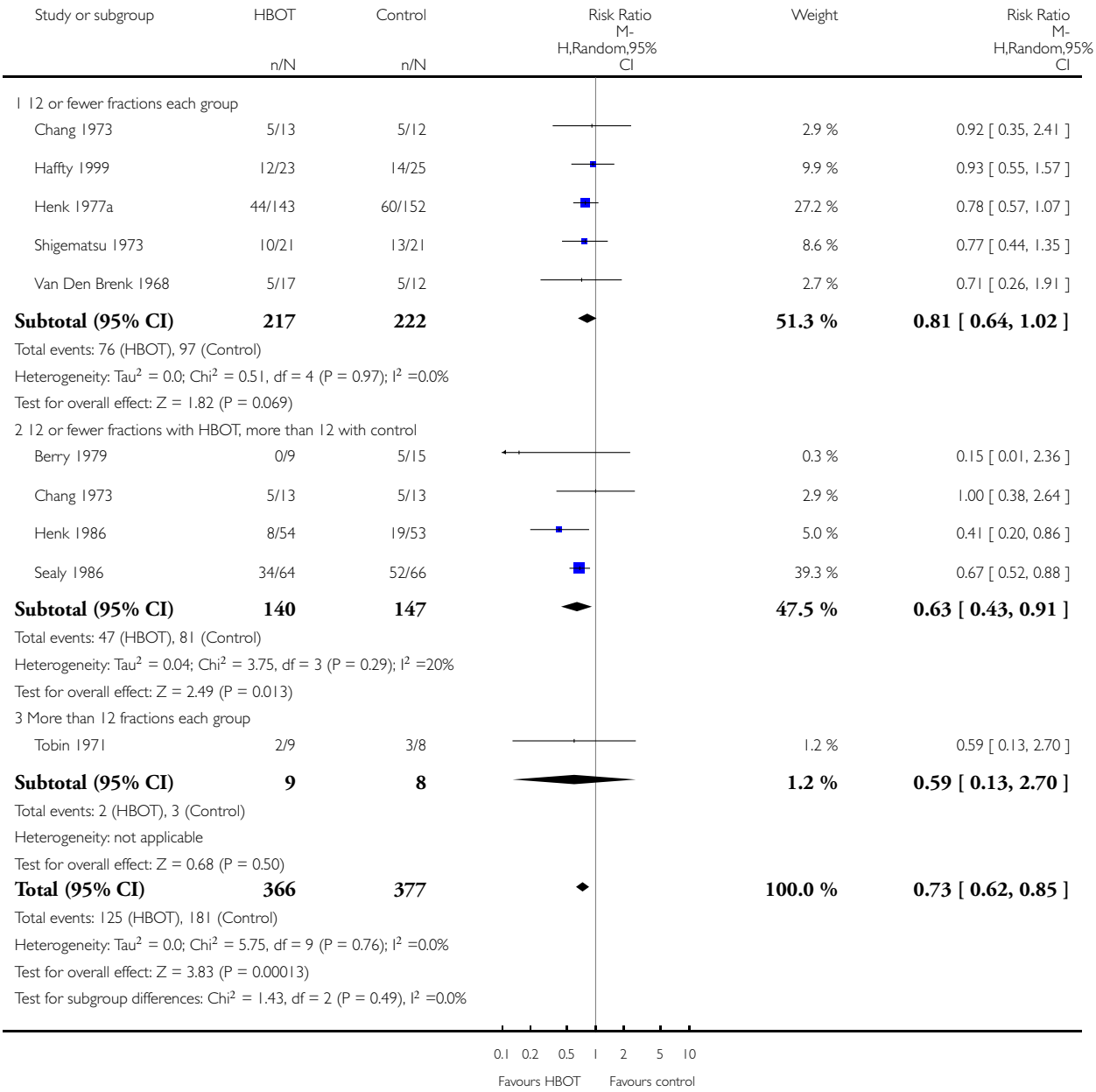
Analysis 1.2. Comparison 1 Death at one year, Outcome 2 Head and neck - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 2 Head and neck - best case scenario



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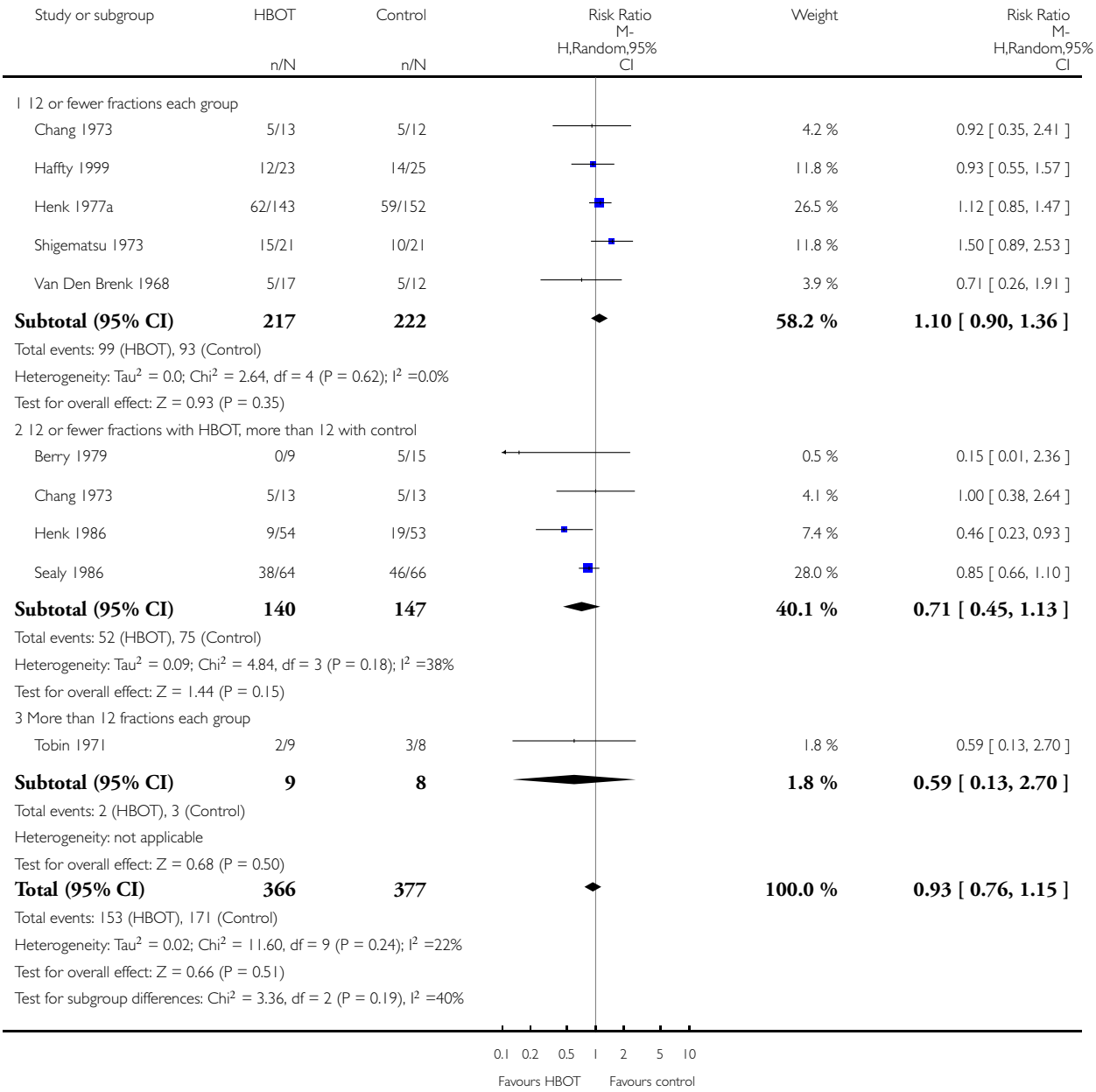
Analysis 1.3. Comparison 1 Death at one year, Outcome 3 Head and neck - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 3 Head and neck - worst case scenario



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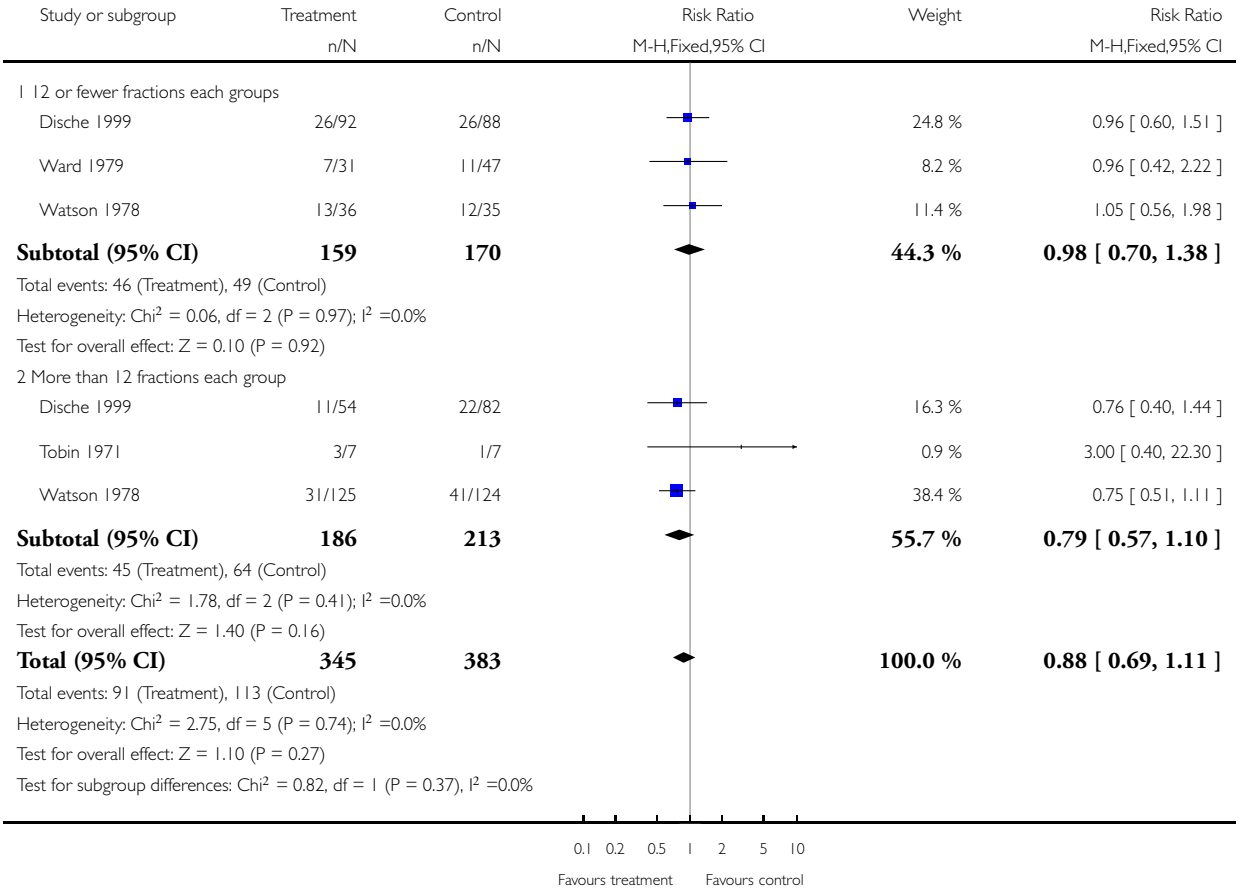
Analysis 1.4. Comparison 1 Death at one year, Outcome 4 Uterine cervix cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 4 Uterine cervix cancer



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Analysis 1.5. Comparison 1 Death at one year, Outcome 5 Uterine cervix - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 5 Uterine cervix - best case scenario

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dische 1999	37/146	48/170		40.8 %	0.90 [0.62, 1.30]
Tobin 1971	3/7	1/7		0.9 %	3.00 [0.40, 22.30]
Ward 1979	7/34	12/48		9.2 %	0.82 [0.36, 1.87]
Watson 1978	44/161	53/159		49.1 %	0.82 [0.59, 1.15]
Total (95% CI)	**348**	**384**		**100.0 %**	**0.87 [0.69, 1.10]**

Total events: 91 (HBOT), 114 (Control)

Heterogeneity: $Chi^2 = 1.63$, df = 3 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 1.14 (P = 0.25)

Test for subgroup differences: Not applicable

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Analysis 1.6. Comparison 1 Death at one year, Outcome 6 Uterine cervix - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 6 Uterine cervix - worst case scenario

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dische 1999	37/146	48/170		41.1 %	0.90 [0.62, 1.30]
Tobin 1971	3/7	1/7		0.9 %	3.00 [0.40, 22.30]
Ward 1979	10/34	11/48		8.5 %	1.28 [0.62, 2.68]
Watson 1978	44/161	53/159		49.5 %	0.82 [0.59, 1.15]
Total (95% CI)	**348**	**384**		**100.0 %**	**0.91 [0.72, 1.15]**

Total events: 94 (HBOT), 113 (Control)

Heterogeneity: $Chi^2 = 2.58$, df = 3 (P = 0.46); $I^2 = 0.0\%$

Test for overall effect: Z = 0.79 (P = 0.43)

Test for subgroup differences: Not applicable

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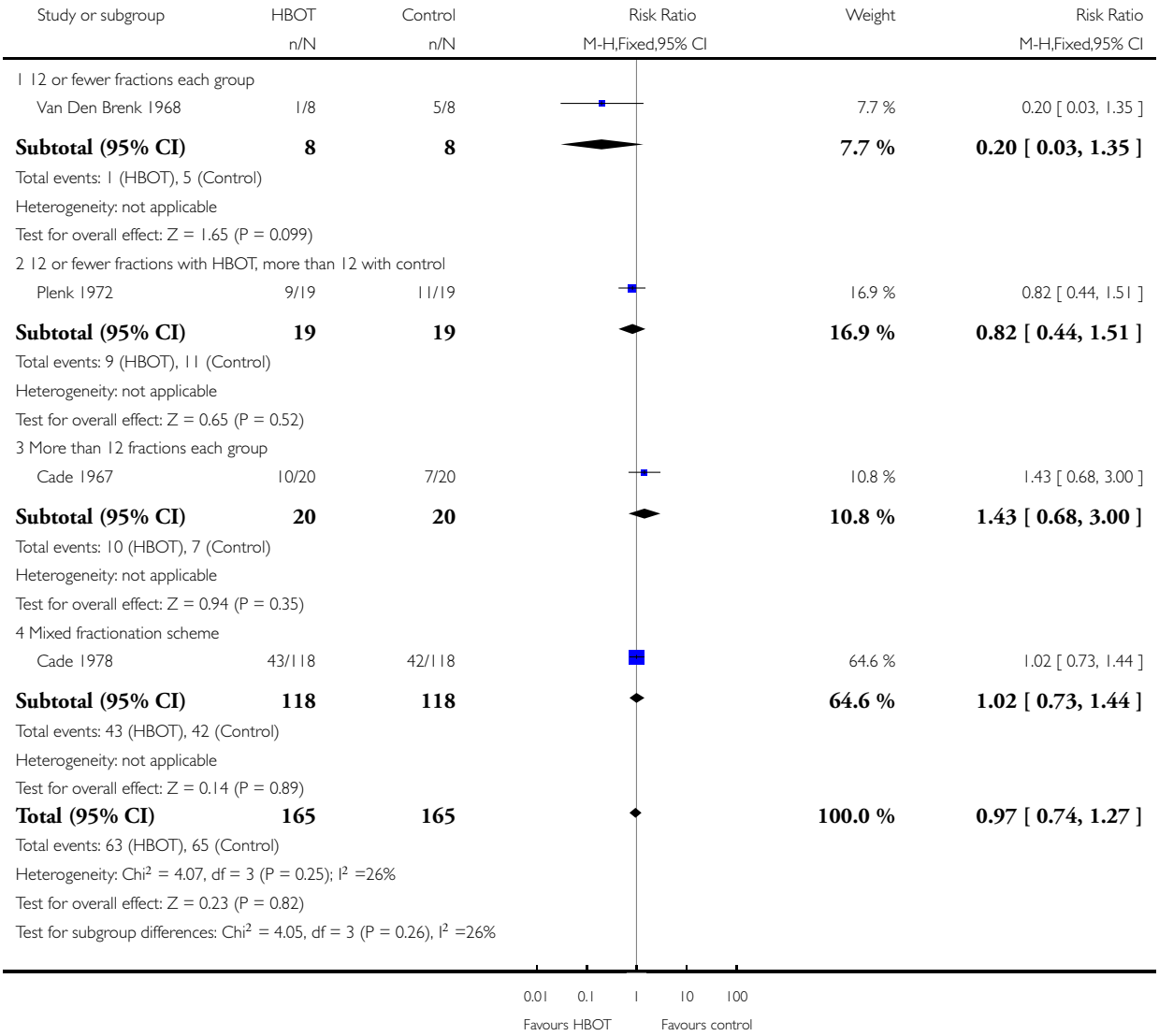
Analysis 1.7. Comparison 1 Death at one year, Outcome 7 Urinary bladder cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 7 Urinary bladder cancer



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Analysis 1.8. Comparison 1 Death at one year, Outcome 8 Urinary bladder - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 8 Urinary bladder - best case scenario

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cade 1967	10/20	7/20		10.2 %	1.43 [0.68, 3.00]
Cade 1978	43/121	44/120		64.5 %	0.97 [0.69, 1.36]
Plenk 1972	9/19	13/21		18.0 %	0.77 [0.43, 1.37]
Van Den Brenk 1968	1/8	5/8		7.3 %	0.20 [0.03, 1.35]
Total (95% CI)	**168**	**169**		**100.0 %**	**0.92 [0.71, 1.21]**

Total events: 63 (HBOT), 69 (Control)

Heterogeneity: $Chi^2 = 4.28$, df = 3 (P = 0.23); $I^2 = 30\%$

Test for overall effect: Z = 0.59 (P = 0.56)

Test for subgroup differences: Not applicable

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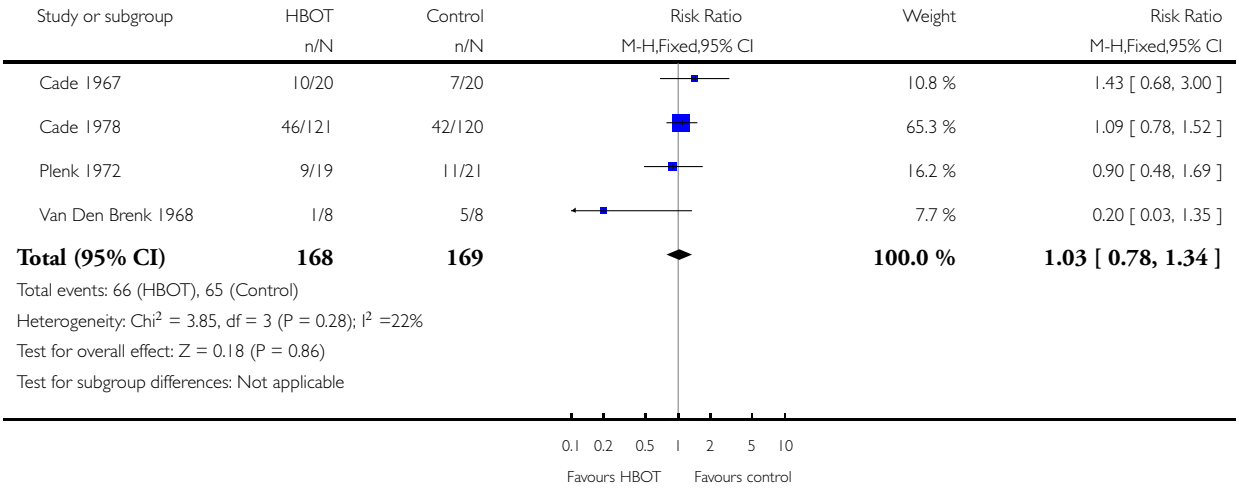
Analysis 1.9. Comparison 1 Death at one year, Outcome 9 Urinary bladder - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 9 Urinary bladder - worst case scenario

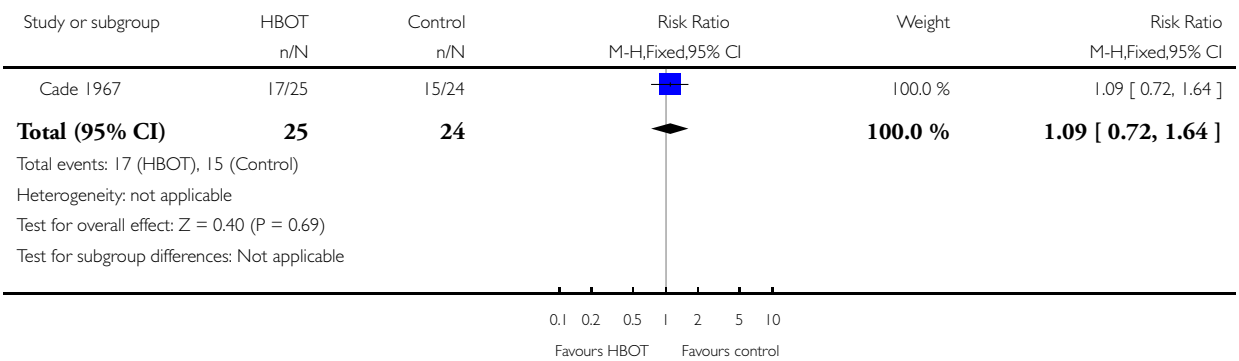


Analysis 1.10. Comparison 1 Death at one year, Outcome 10 Bronchial cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 10 Bronchial cancer



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Analysis 1.11. Comparison 1 Death at one year, Outcome 11 Rectal cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 11 Rectal cancer

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tobin 1971	2/2	1/2		100.0 %	1.67 [0.48, 5.76]
Total (95% CI)	**2**	**2**		**100.0 %**	**1.67 [0.48, 5.76]**

Total events: 2 (HBOT), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.81 (P = 0.42)

Test for subgroup differences: Not applicable

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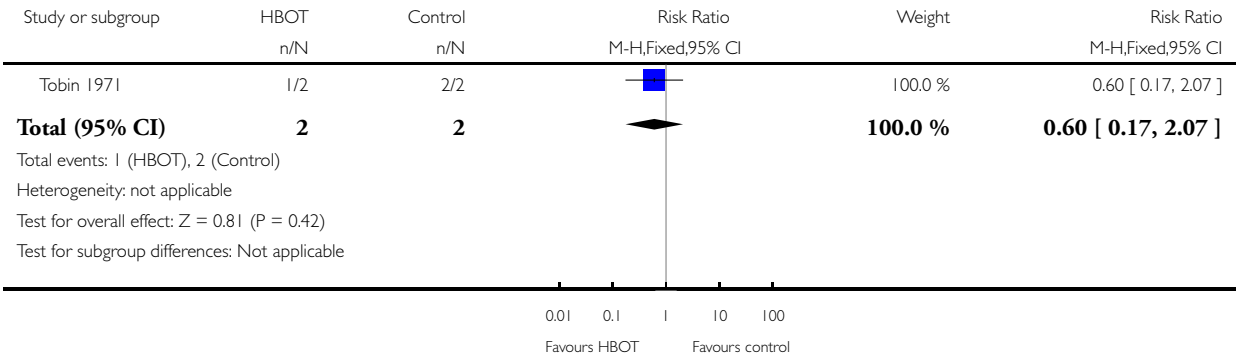
Analysis 1.12. Comparison 1 Death at one year, Outcome 12 Oesophageal cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 12 Oesophageal cancer

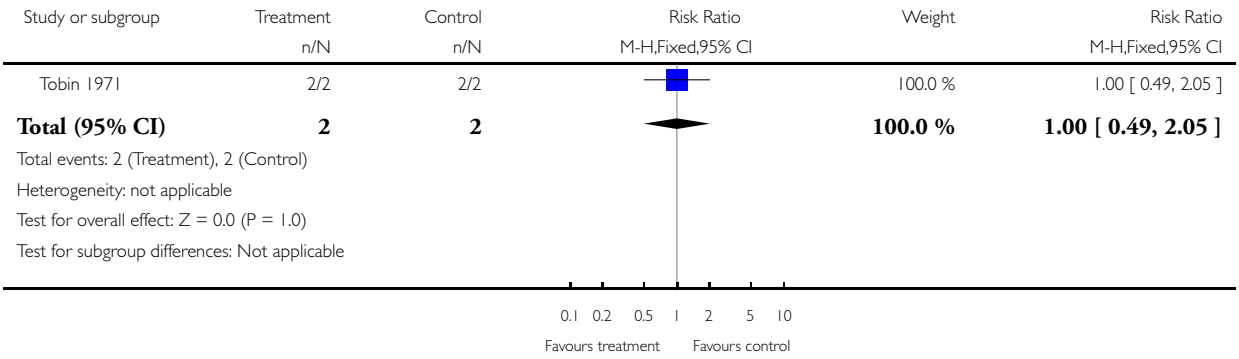


Analysis 1.13. Comparison 1 Death at one year, Outcome 13 Gliobastoma.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 1 Death at one year

Outcome: 13 Gliobastoma



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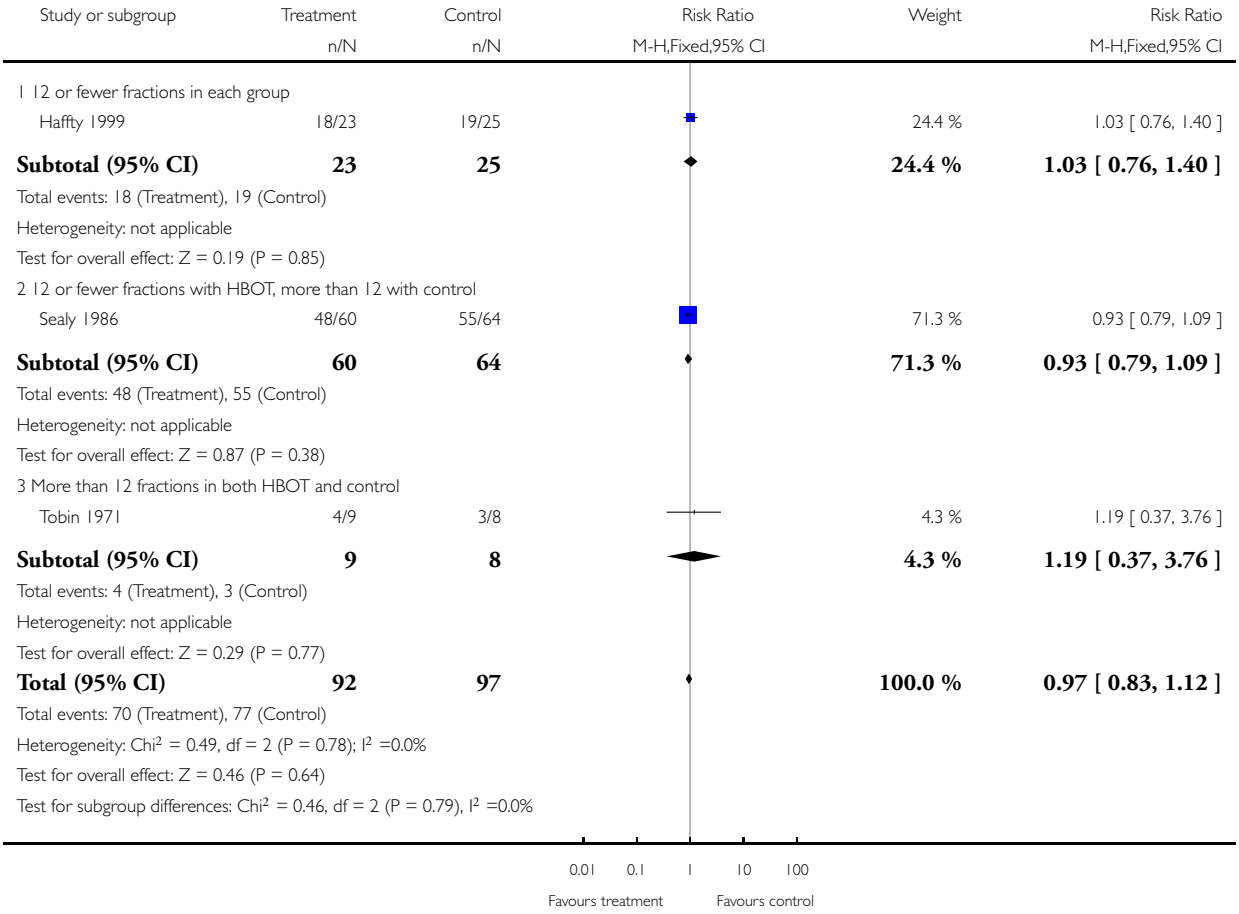
Analysis 2.1. Comparison 2 Death at two years, Outcome 1 Head and neck cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 2 Death at two years

Outcome: 1 Head and neck cancer



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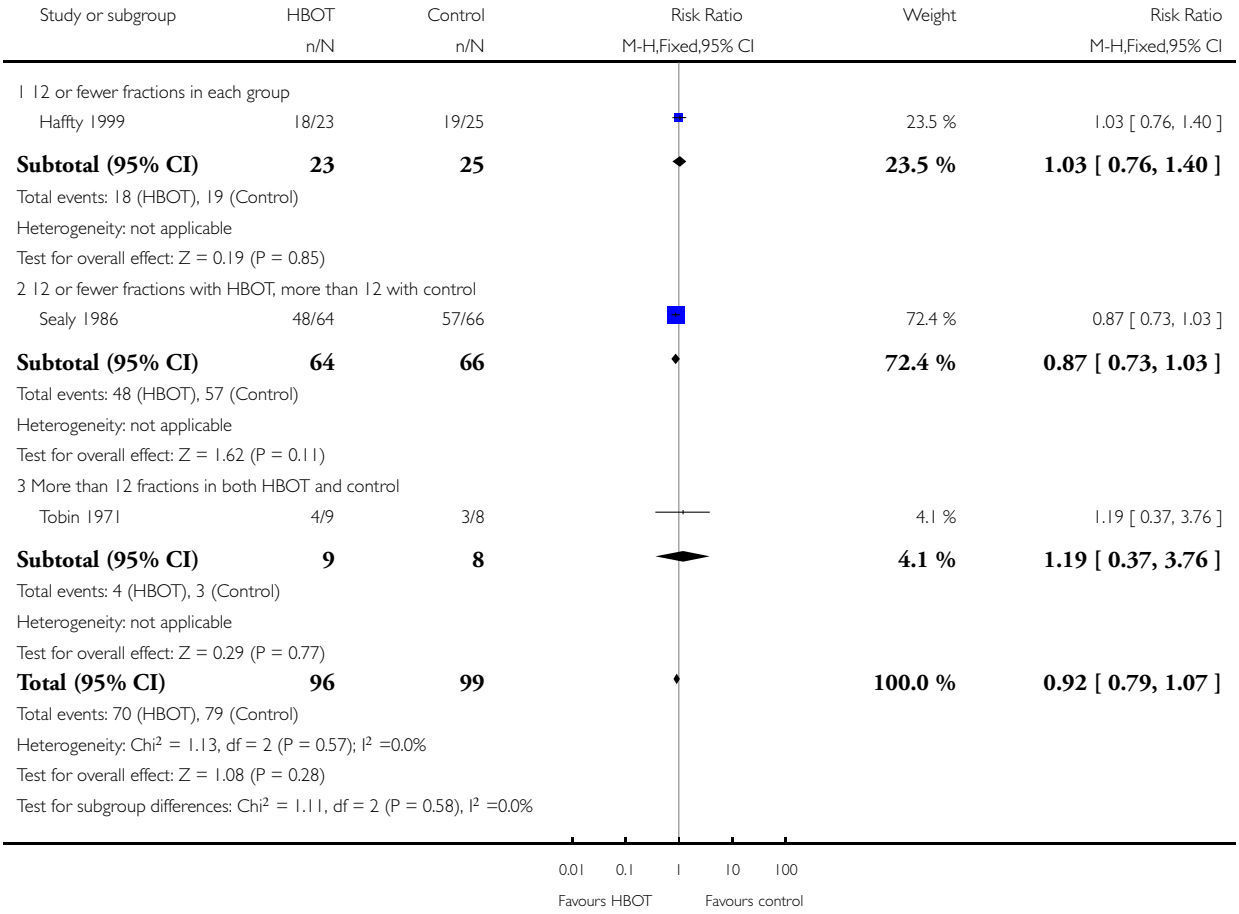
Analysis 2.2. Comparison 2 Death at two years, Outcome 2 Head and neck - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 2 Death at two years

Outcome: 2 Head and neck - best case scenario



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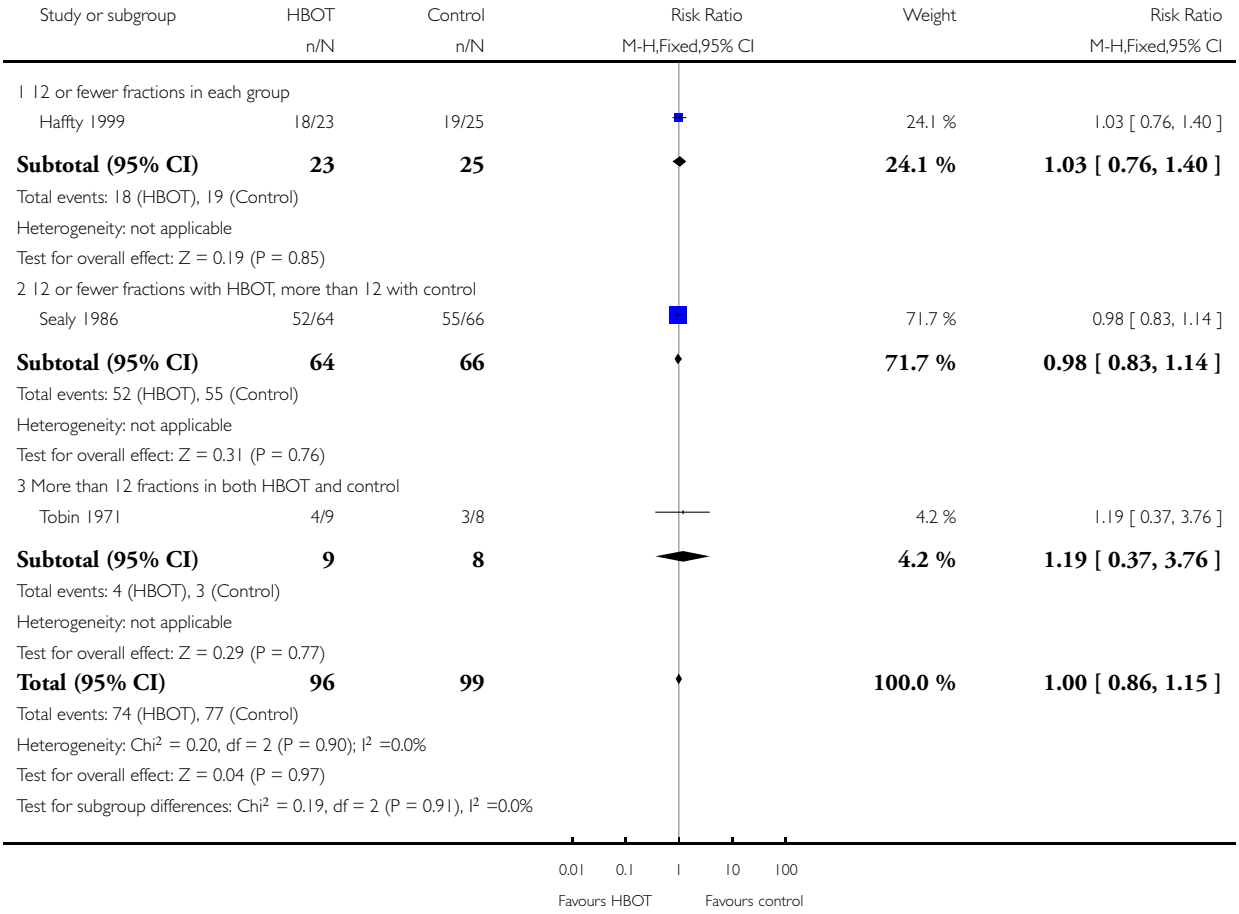
Analysis 2.3. Comparison 2 Death at two years, Outcome 3 Head and neck - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 2 Death at two years

Outcome: 3 Head and neck - worst case scenario



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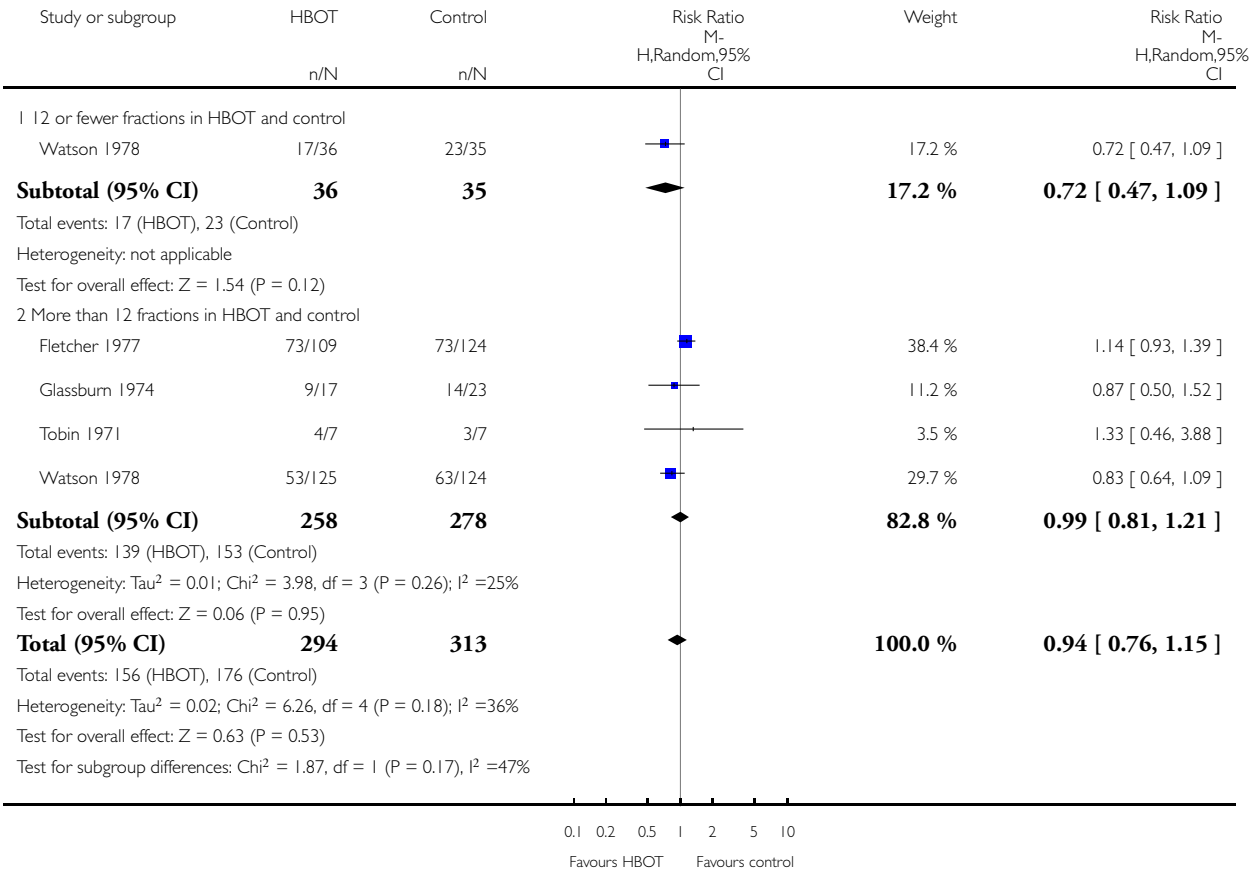
Analysis 2.4. Comparison 2 Death at two years, Outcome 4 Uterine cervix cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 2 Death at two years

Outcome: 4 Uterine cervix cancer



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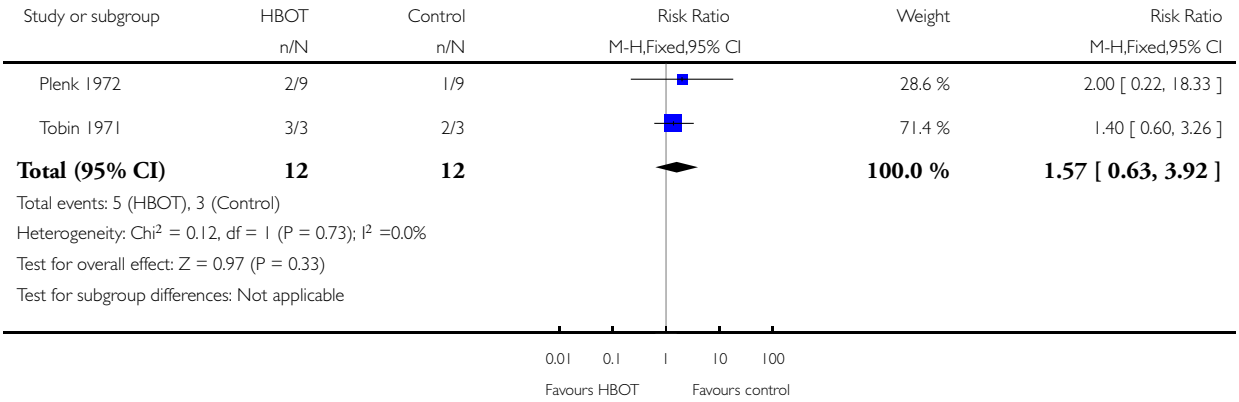
Analysis 2.5. Comparison 2 Death at two years, Outcome 5 Urinary bladder carcinoma.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 2 Death at two years

Outcome: 5 Urinary bladder carcinoma

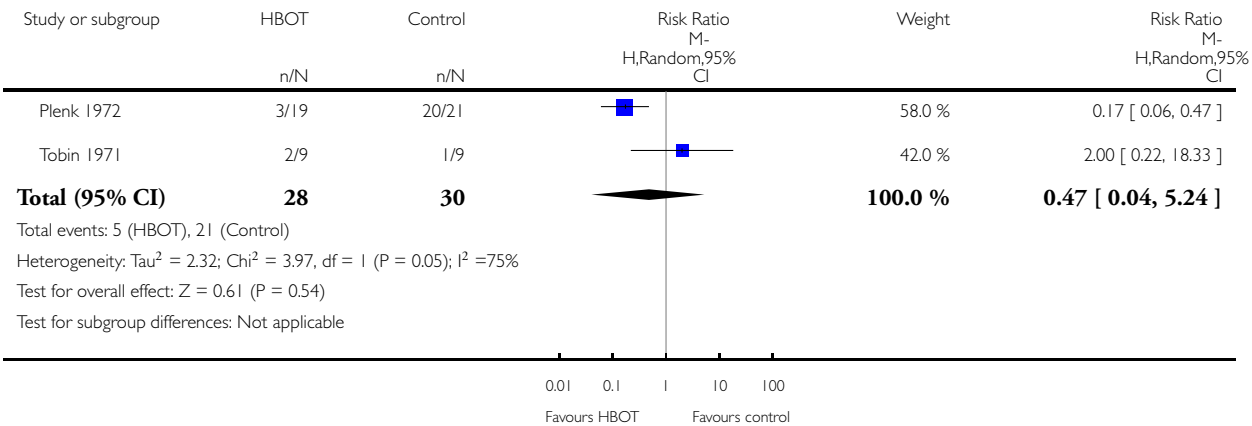


Analysis 2.6. Comparison 2 Death at two years, Outcome 6 Urinary bladder - best case.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 2 Death at two years

Outcome: 6 Urinary bladder - best case



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Analysis 2.7. Comparison 2 Death at two years, Outcome 7 Urinary bladder - worst case.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 2 Death at two years

Outcome: 7 Urinary bladder - worst case

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Plenk 1972	19/19	3/21		76.9 %	6.13 [2.34, 16.06]
Tobin 1971	2/9	1/9		23.1 %	2.00 [0.22, 18.33]
Total (95% CI)	**28**	**30**		**100.0 %**	**5.18 [2.18, 12.31]**

Total events: 21 (HBOT), 4 (Control)

Heterogeneity: $Chi^2 = 0.83$, df = 1 (P = 0.36); $I^2 = 0.0\%$

Test for overall effect: Z = 3.72 (P = 0.00020)

Test for subgroup differences: Not applicable

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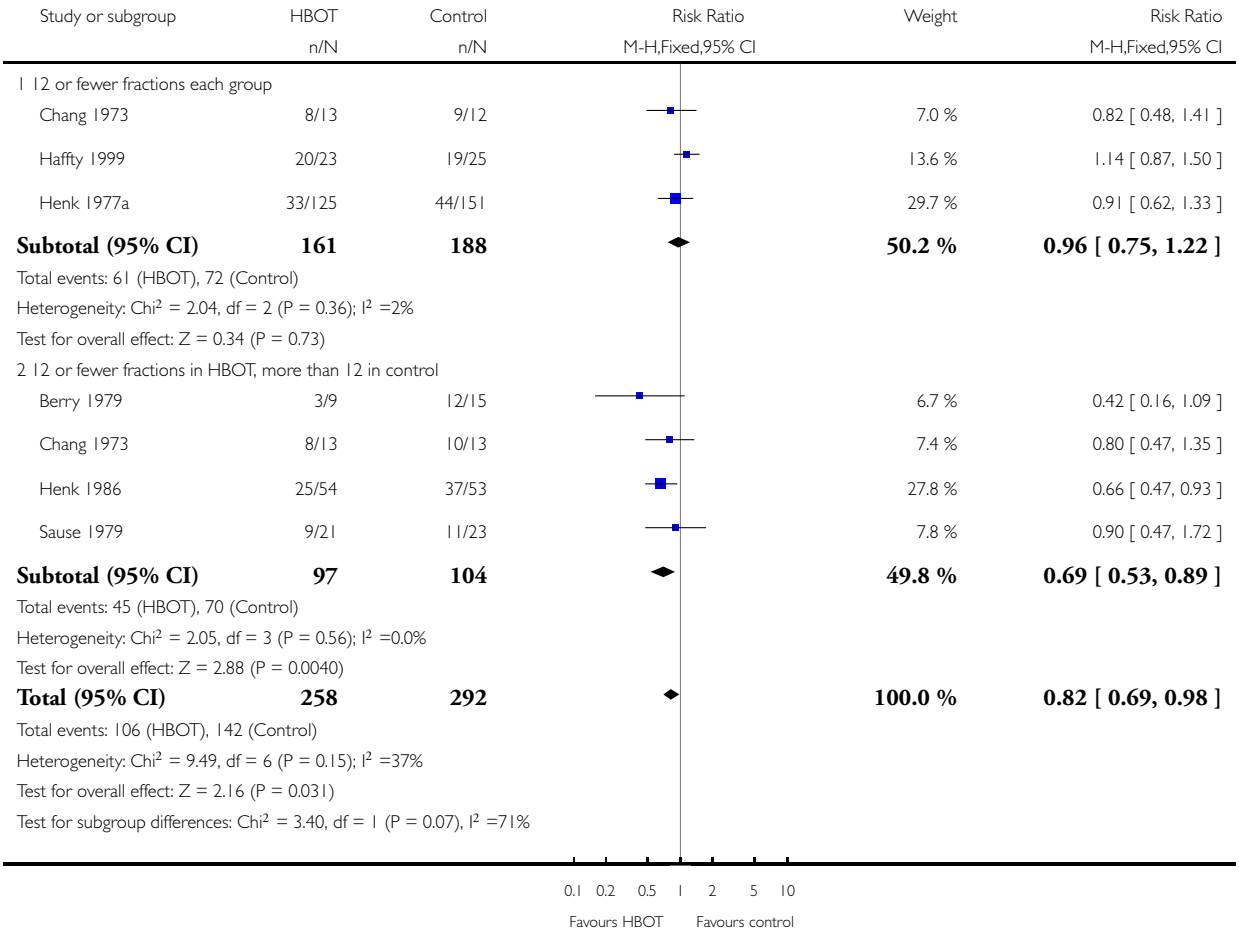
Analysis 3.1. Comparison 3 Death at five years, Outcome 1 Head and neck cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 3 Death at five years

Outcome: 1 Head and neck cancer



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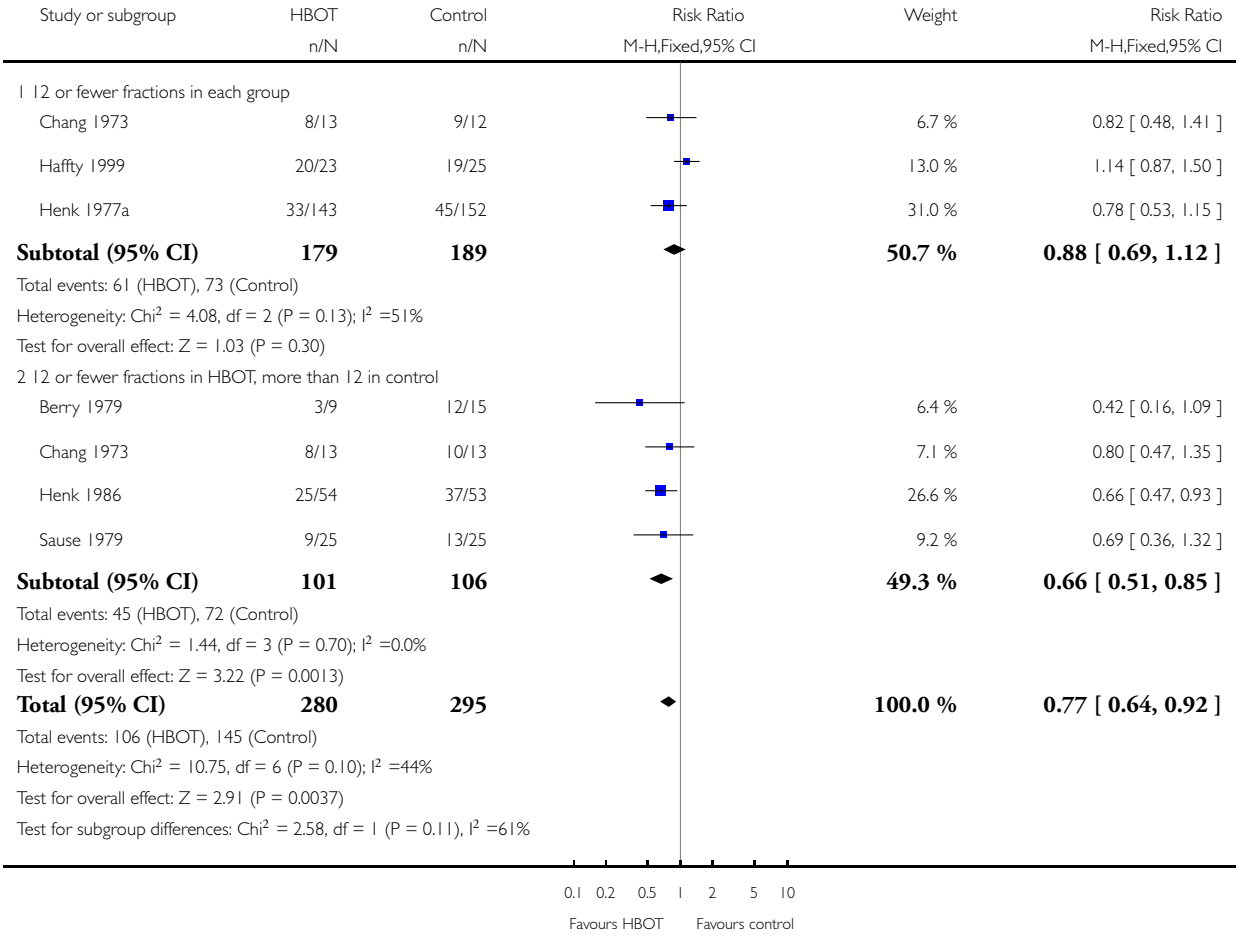
Analysis 3.2. Comparison 3 Death at five years, Outcome 2 Head and neck - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 3 Death at five years

Outcome: 2 Head and neck - best case scenario



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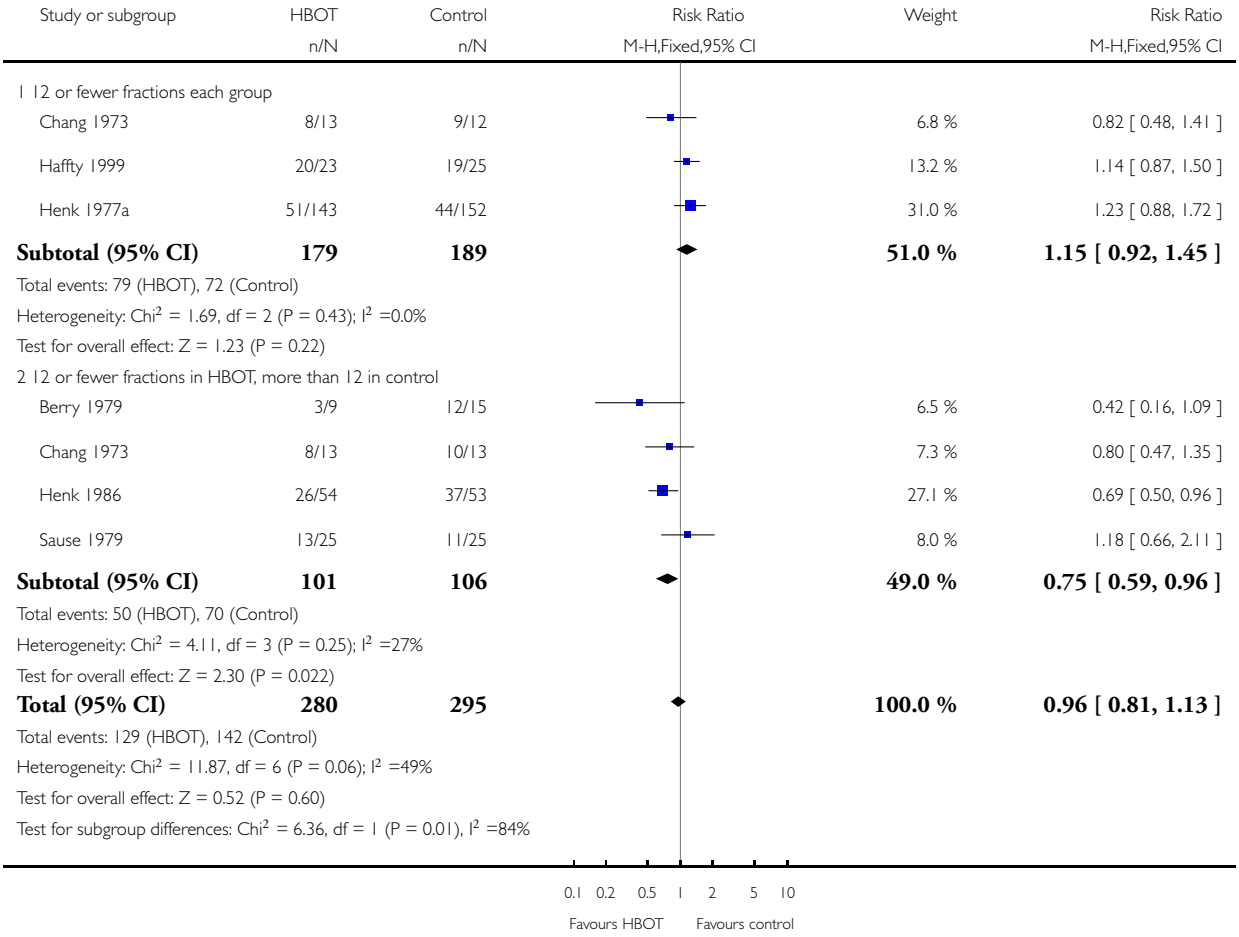
Analysis 3.3. Comparison 3 Death at five years, Outcome 3 Head and neck - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 3 Death at five years

Outcome: 3 Head and neck - worst case scenario



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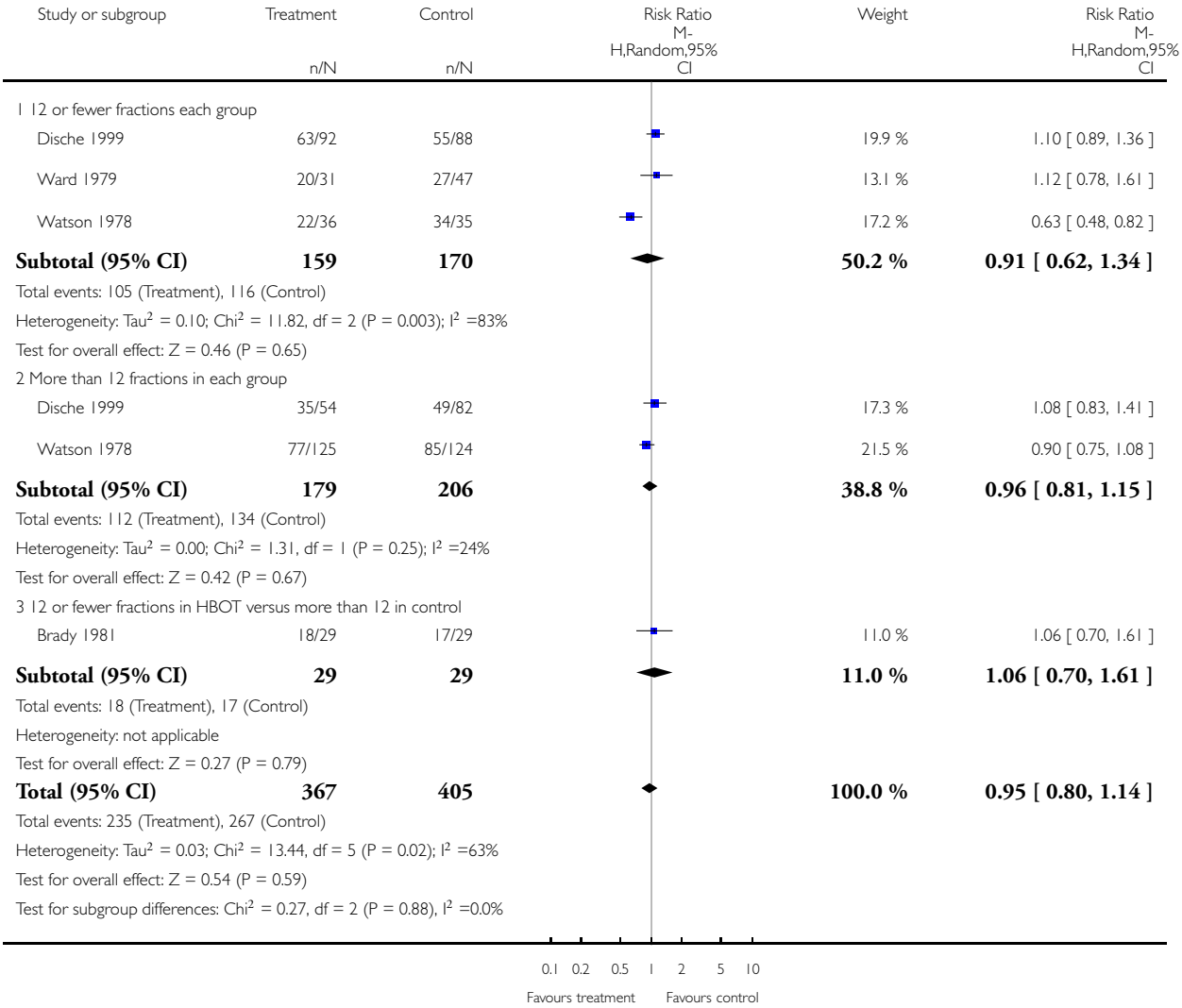
Analysis 3.4. Comparison 3 Death at five years, Outcome 4 Uterine cervix cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 3 Death at five years

Outcome: 4 Uterine cervix cancer



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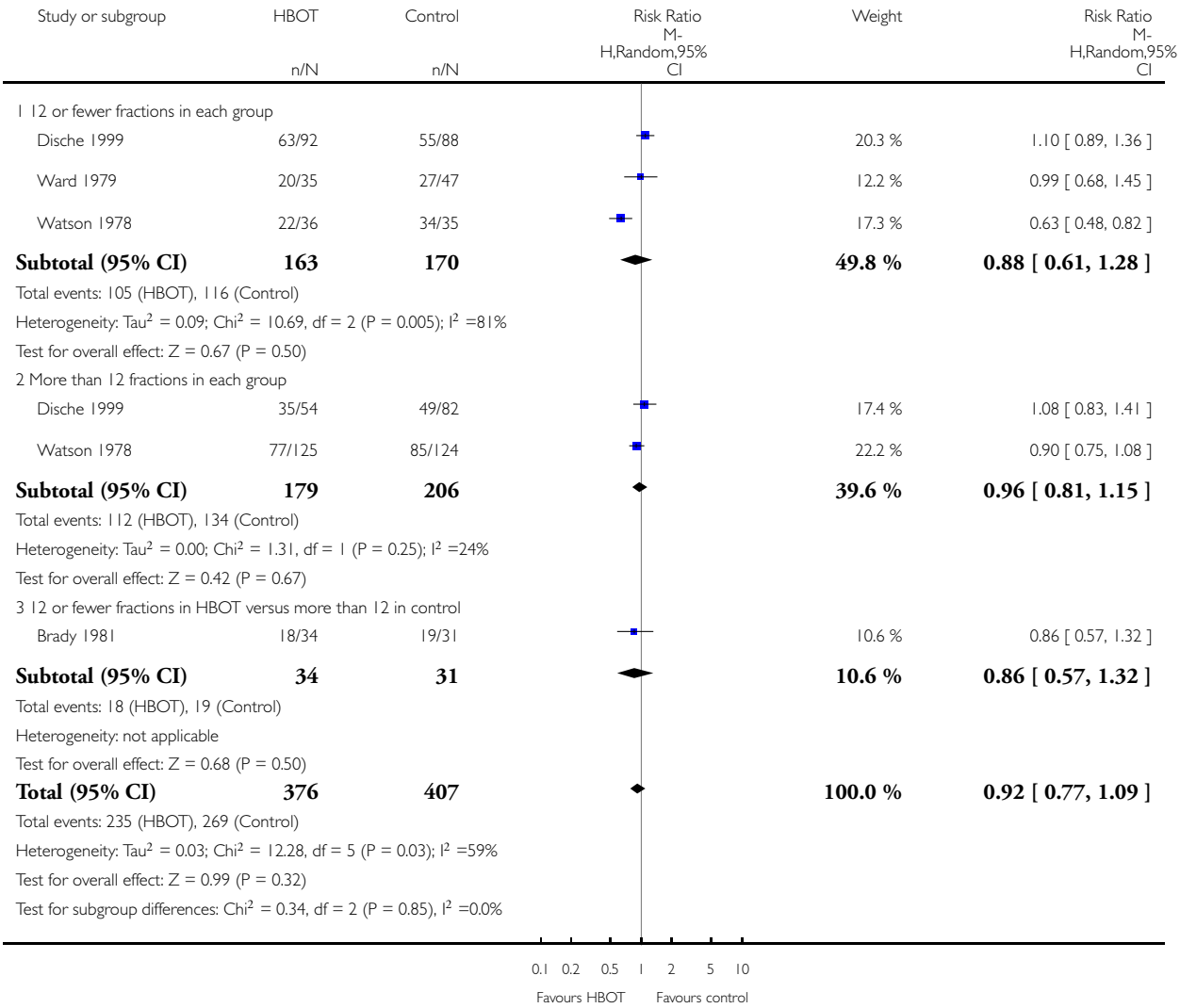
Analysis 3.5. Comparison 3 Death at five years, Outcome 5 Uterine cancer - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 3 Death at five years

Outcome: 5 Uterine cancer - best case scenario



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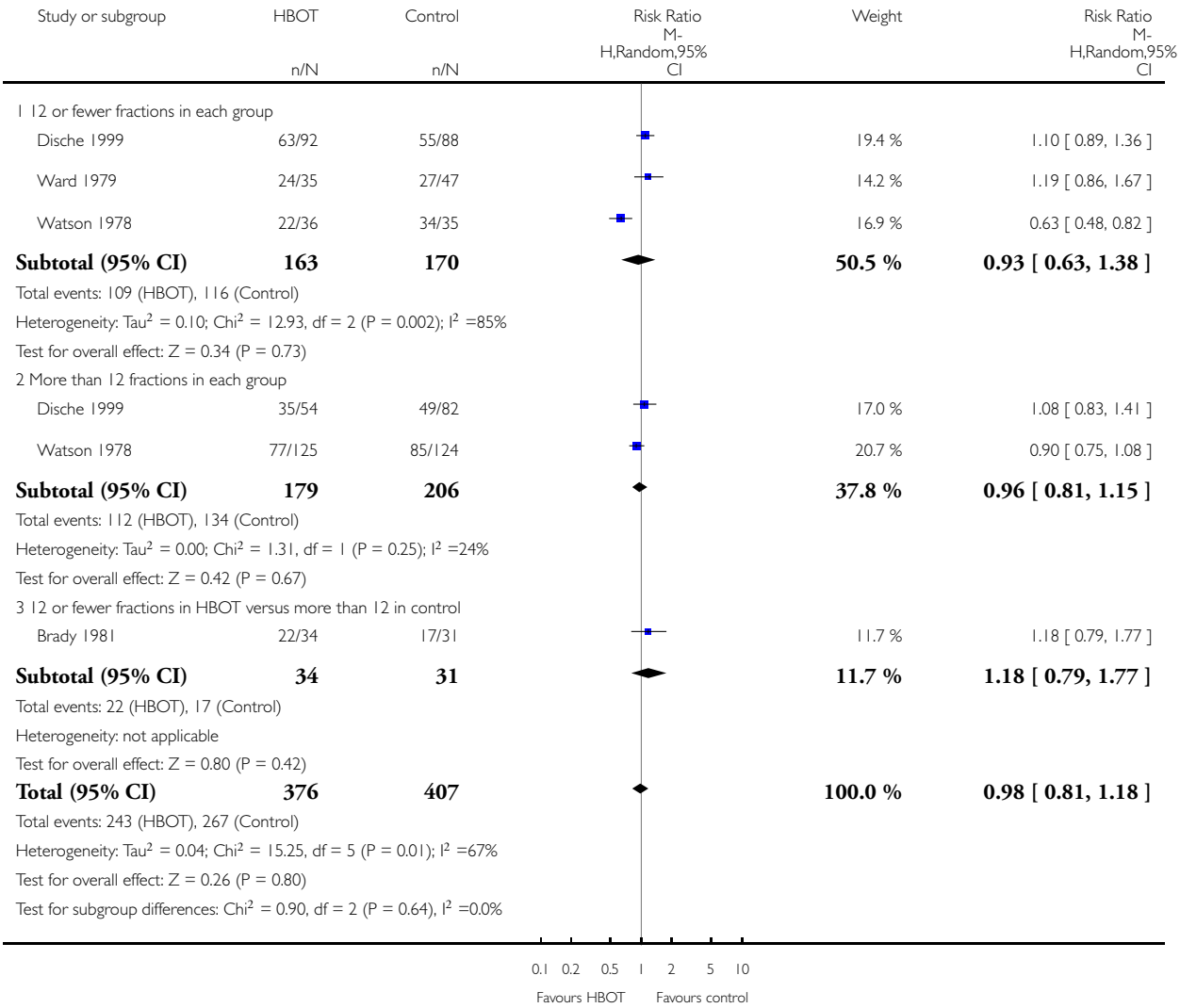
Analysis 3.6. Comparison 3 Death at five years, Outcome 6 Uterine cancer - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 3 Death at five years

Outcome: 6 Uterine cancer - worst case scenario



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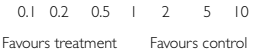
Analysis 3.7. Comparison 3 Death at five years, Outcome 7 Urinary bladder cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 3 Death at five years

Outcome: 7 Urinary bladder cancer

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cade 1978	85/118	82/118		100.0 %	1.04 [0.88, 1.22]
Total (95% CI)	**118**	**118**		**100.0 %**	**1.04 [0.88, 1.22]**
Total events: 85 (Treatment), 82 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
Test for subgroup differences: Not applicable					



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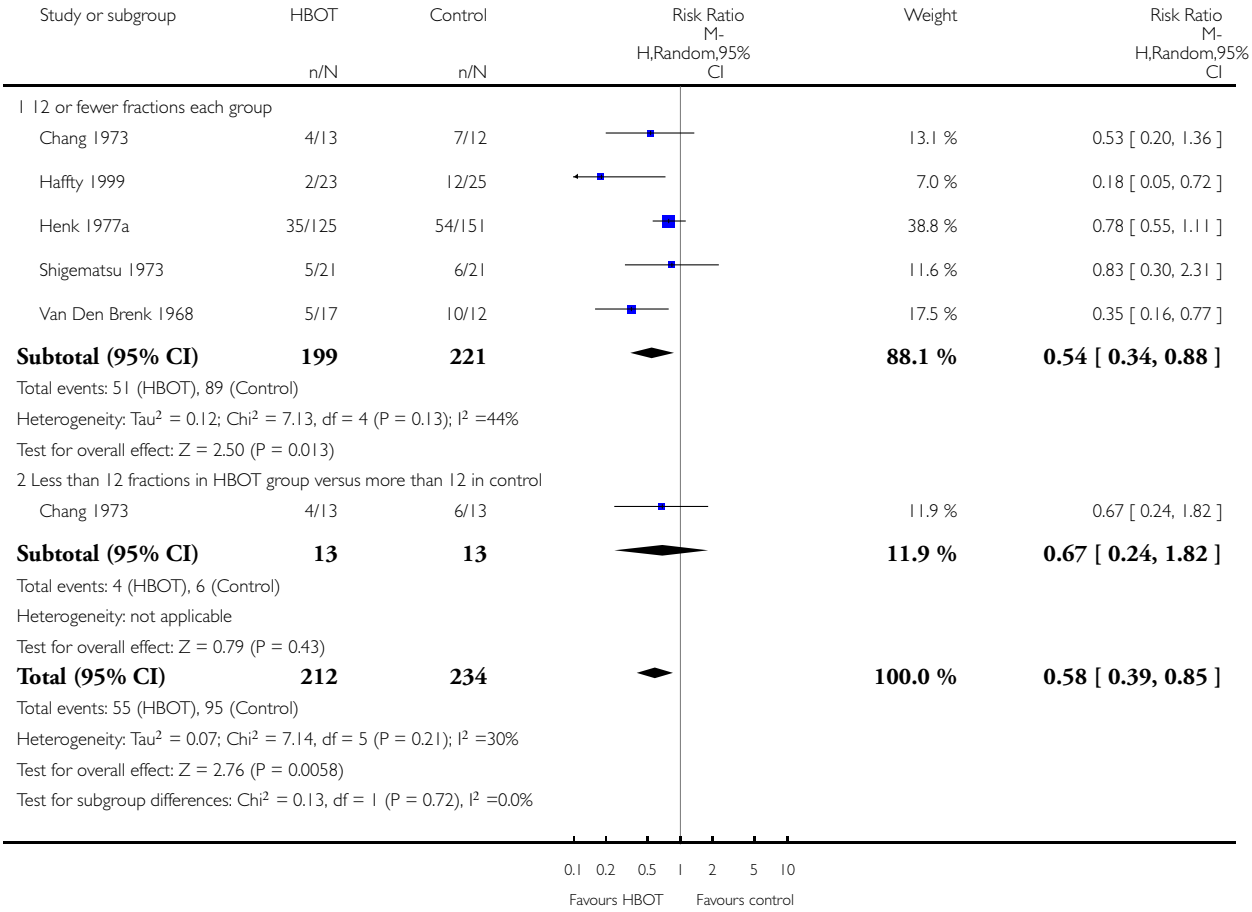
Analysis 4.1. Comparison 4 Failure to control local tumour at three months, Outcome 1 Head and neck cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 4 Failure to control local tumour at three months

Outcome: 1 Head and neck cancer



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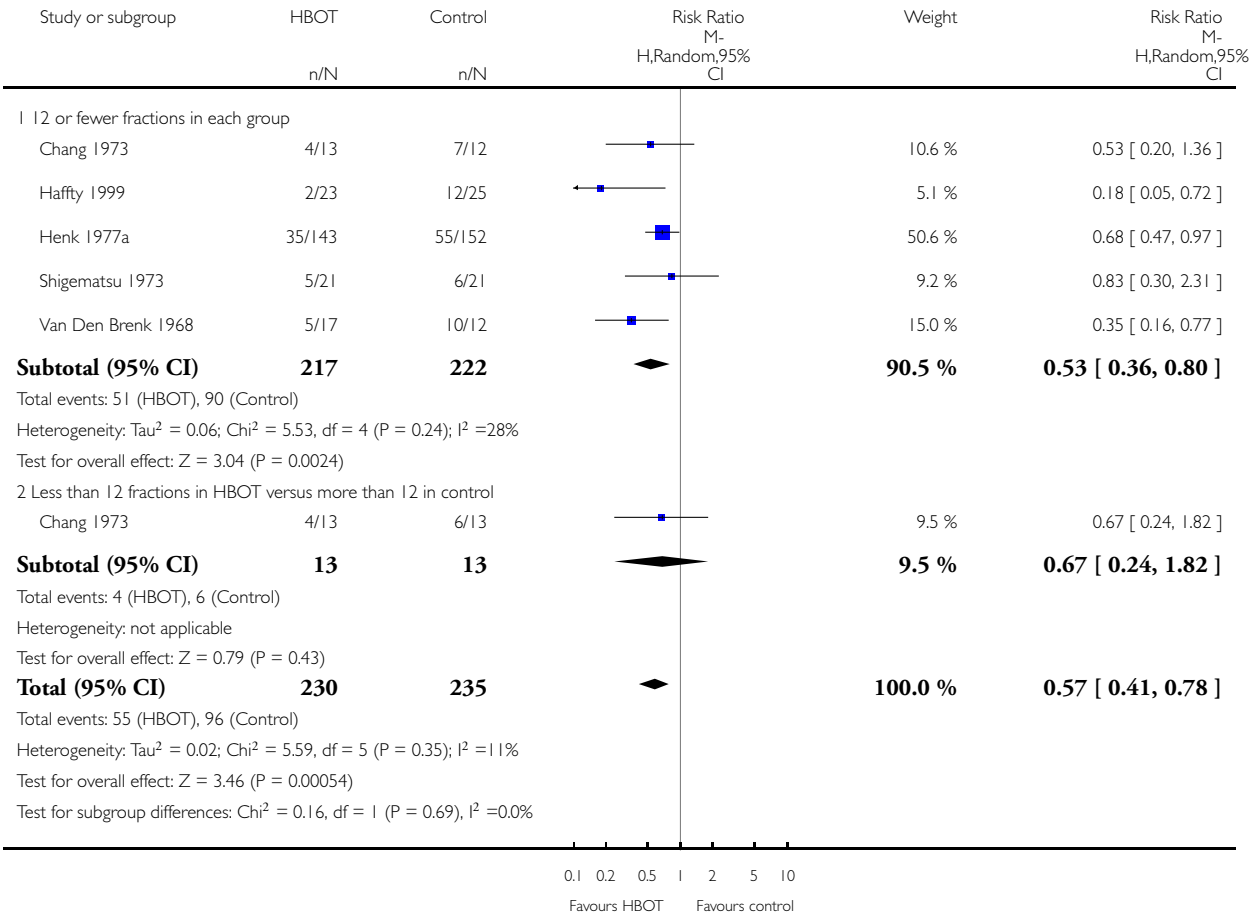
Analysis 4.2. Comparison 4 Failure to control local tumour at three months, Outcome 2 Head and neck cancer - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 4 Failure to control local tumour at three months

Outcome: 2 Head and neck cancer - best case scenario



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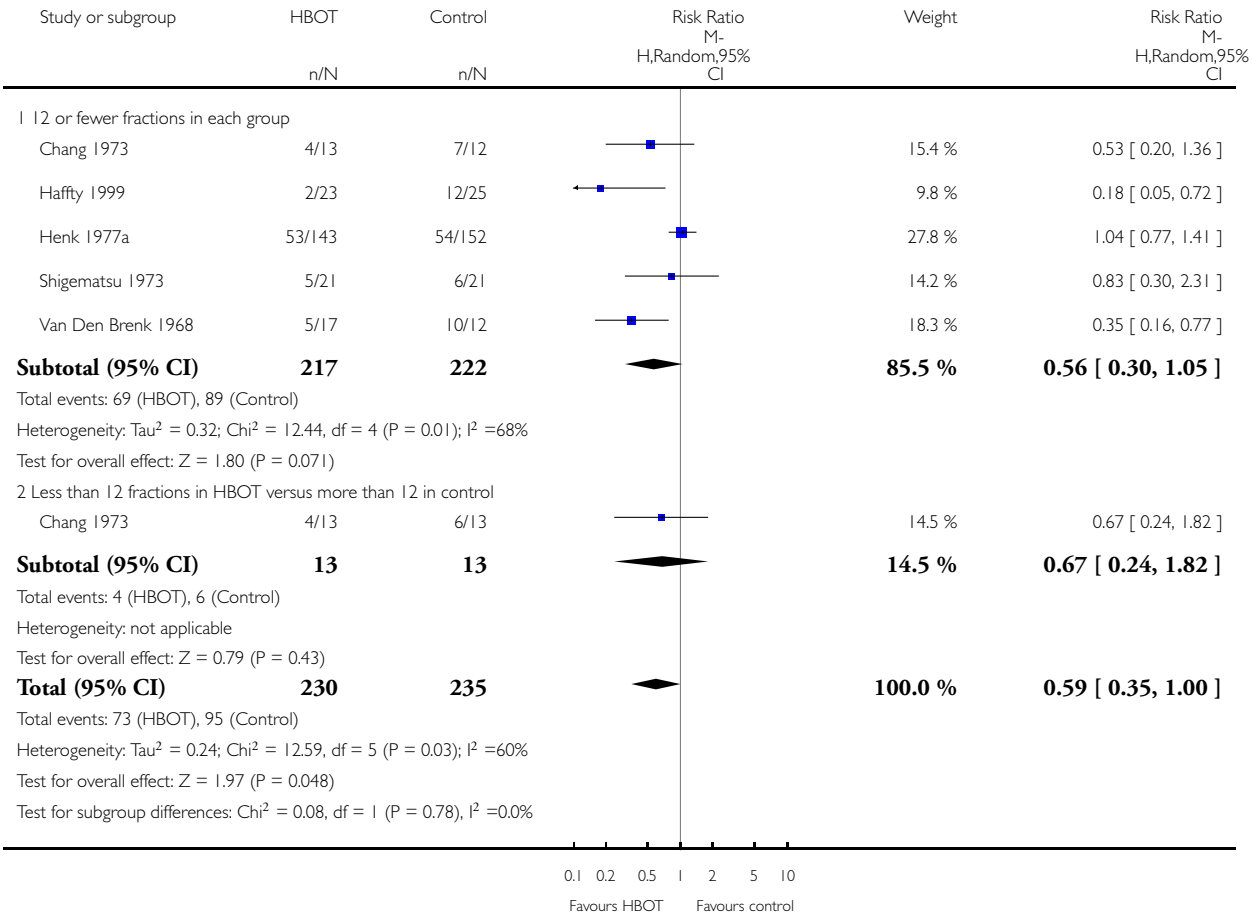
Analysis 4.3. Comparison 4 Failure to control local tumour at three months, Outcome 3 Head and neck - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 4 Failure to control local tumour at three months

Outcome: 3 Head and neck - worst case scenario



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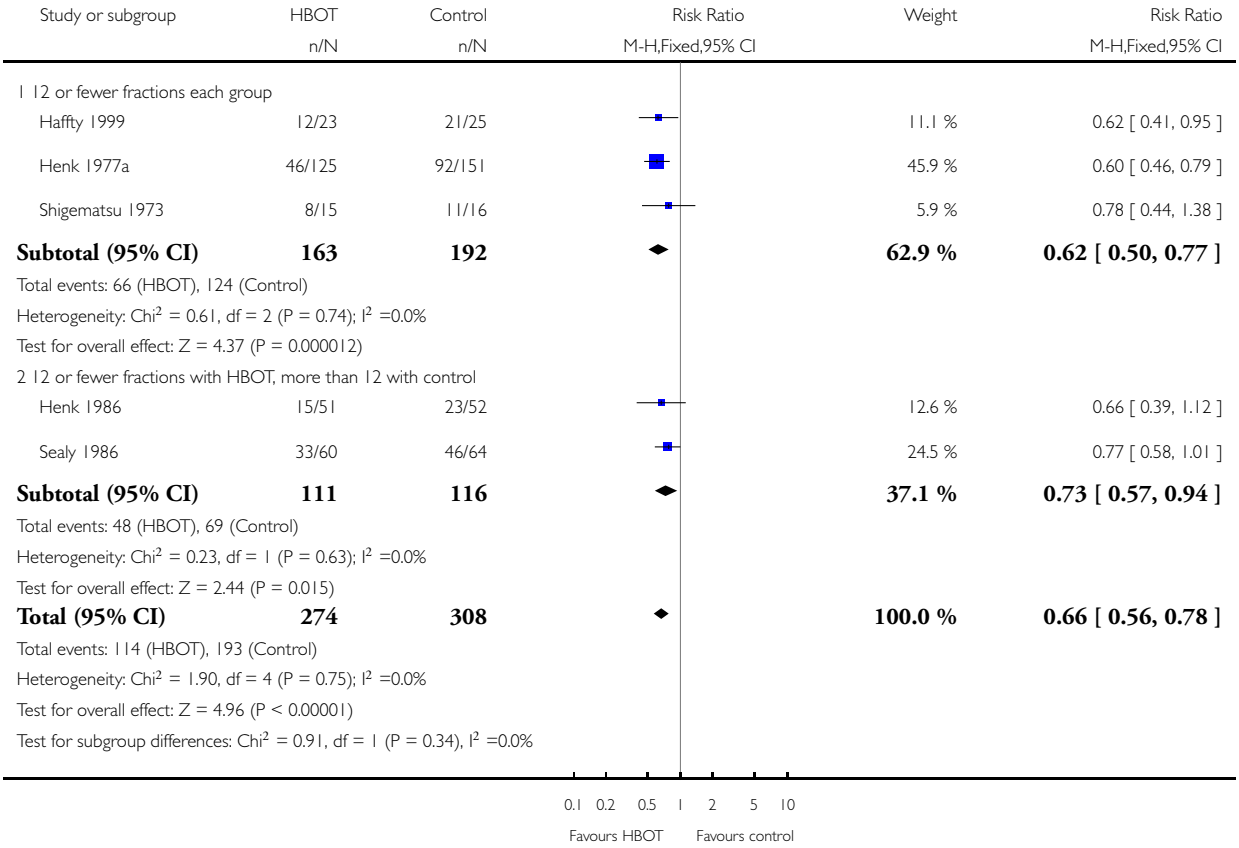
Analysis 5.1. Comparison 5 Local recurrence at one year, Outcome 1 Head and neck cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 5 Local recurrence at one year

Outcome: 1 Head and neck cancer



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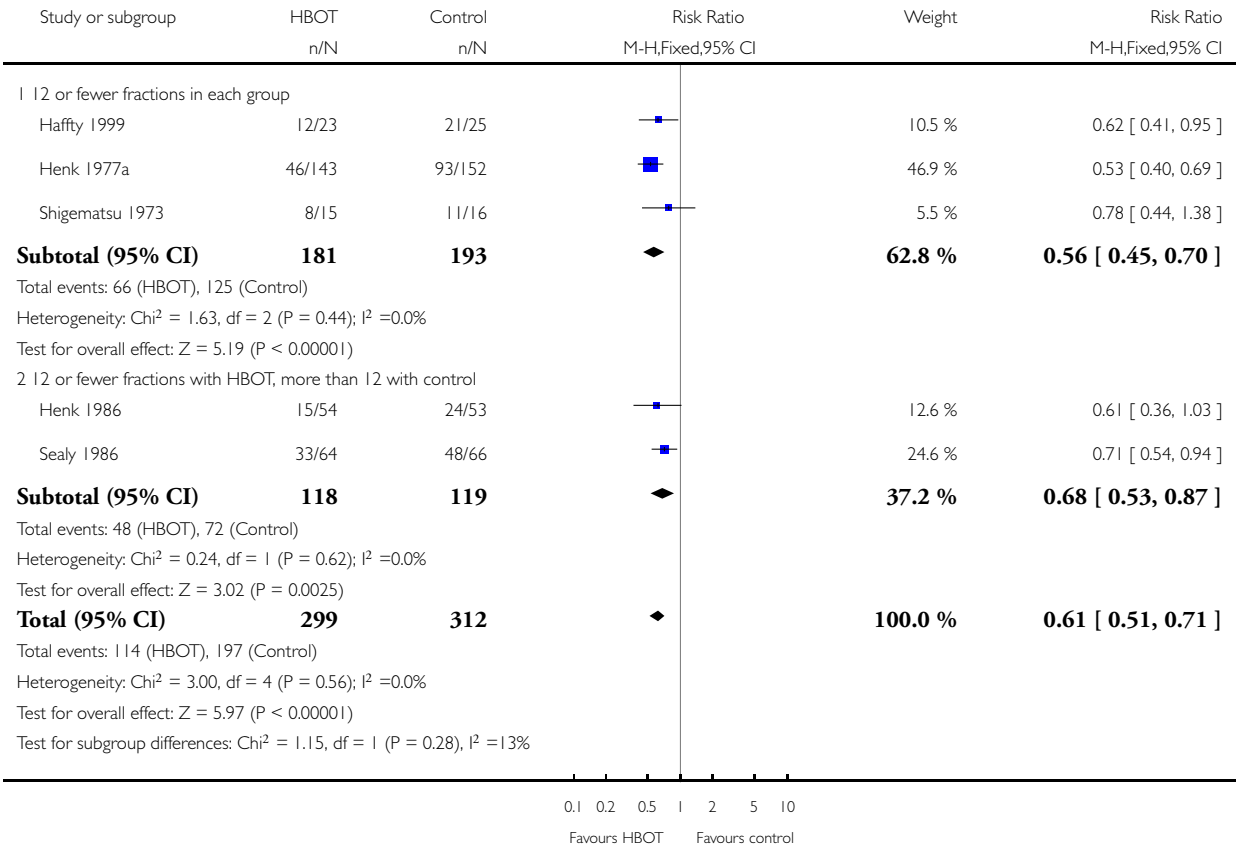
Analysis 5.2. Comparison 5 Local recurrence at one year, Outcome 2 Head and neck cancer - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 5 Local recurrence at one year

Outcome: 2 Head and neck cancer - best case scenario



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Analysis 5.3. Comparison 5 Local recurrence at one year, Outcome 3 Head and neck cancer - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 5 Local recurrence at one year

Outcome: 3 Head and neck cancer - worst case scenario

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 12 or fewer fractions in each group					
Haffty 1999	12/23	21/25		10.7 %	0.62 [0.41, 0.95]
Henk 1977a	64/143	92/152		47.3 %	0.74 [0.59, 0.92]
Shigematsu 1973	8/15	11/16		5.6 %	0.78 [0.44, 1.38]
Subtotal (95% CI)	**181**	**193**		**63.7 %**	**0.72 [0.60, 0.87]**
Total events: 84 (HBOT), 124 (Control)					
Heterogeneity: Chi^2 = 0.58, df = 2 (P = 0.75); I^2 =0.0%					
Test for overall effect: Z = 3.39 (P = 0.00071)					
2 12 or fewer fractions with HBOT, more than 12 with control					
Henk 1986	18/54	23/53		12.3 %	0.77 [0.47, 1.25]
Sealy 1986	37/64	46/66		24.0 %	0.83 [0.64, 1.08]
Subtotal (95% CI)	**118**	**119**		**36.3 %**	**0.81 [0.64, 1.03]**
Total events: 55 (HBOT), 69 (Control)					
Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 1.75 (P = 0.081)					
Total (95% CI)	**299**	**312**		**100.0 %**	**0.75 [0.65, 0.87]**
Total events: 139 (HBOT), 193 (Control)					
Heterogeneity: Chi^2 = 1.34, df = 4 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 3.75 (P = 0.00018)					
Test for subgroup differences: Chi^2 = 0.53, df = 1 (P = 0.47), I^2 =0.0%					

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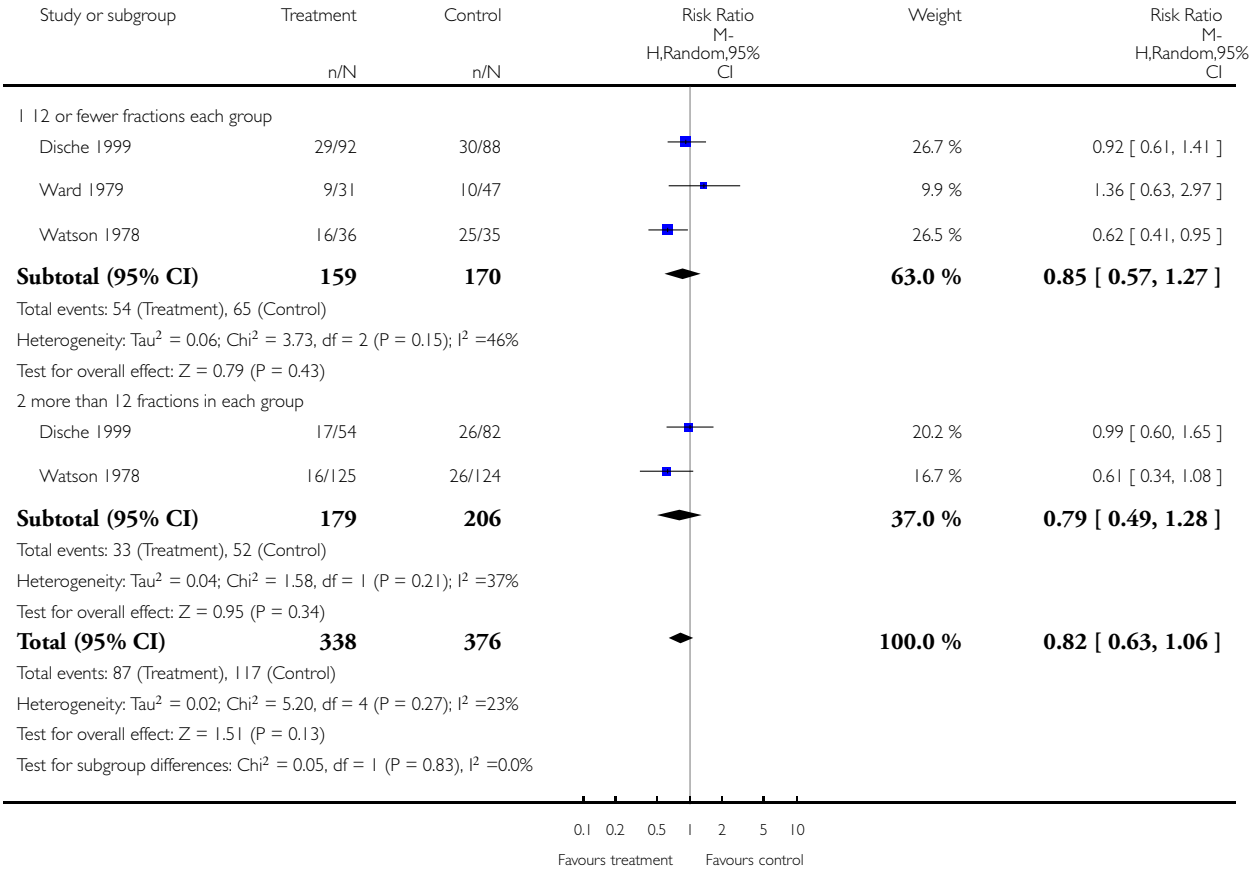
Analysis 5.4. Comparison 5 Local recurrence at one year, Outcome 4 Uterine cervix cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 5 Local recurrence at one year

Outcome: 4 Uterine cervix cancer



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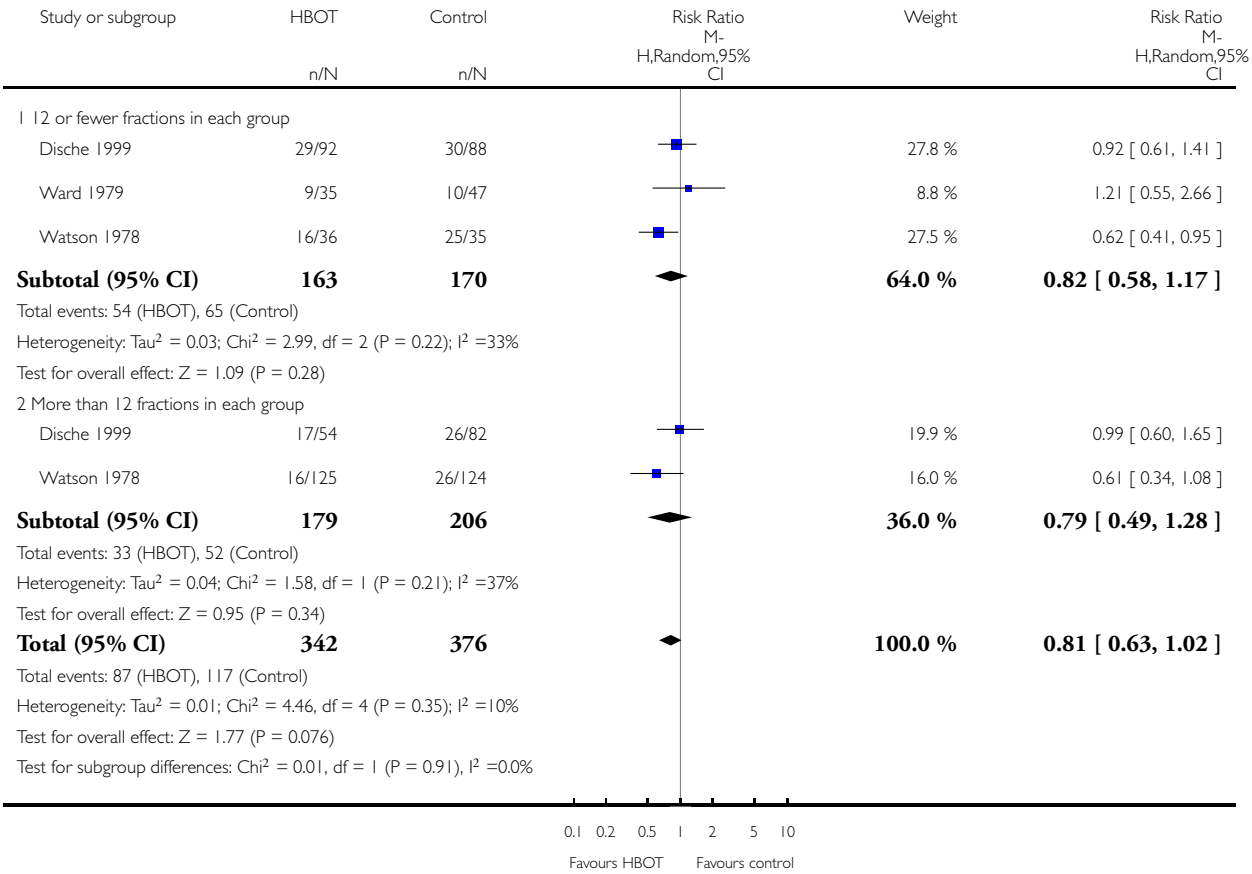
Analysis 5.5. Comparison 5 Local recurrence at one year, Outcome 5 Uterine cervix cancer - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 5 Local recurrence at one year

Outcome: 5 Uterine cervix cancer - best case scenario



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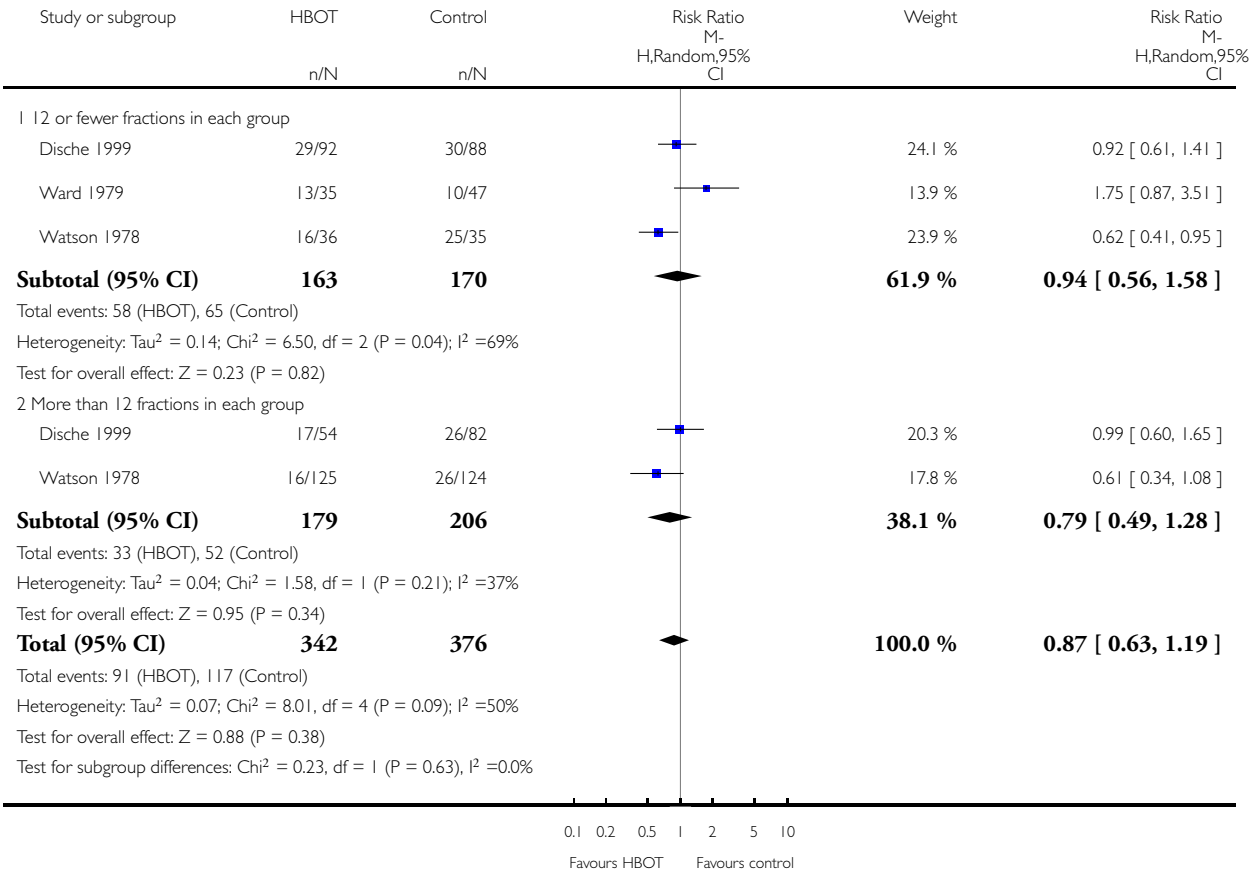
Analysis 5.6. Comparison 5 Local recurrence at one year, Outcome 6 Uterine cervix cancer - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 5 Local recurrence at one year

Outcome: 6 Uterine cervix cancer - worst case scenario



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Analysis 6.1. Comparison 6 Local recurrence at two years, Outcome 1 Head and neck cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 6 Local recurrence at two years

Outcome: 1 Head and neck cancer

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Haffty 1999	16/23	21/25		100.0 %	0.83 [0.60, 1.14]
Total (95% CI)	**23**	**25**		**100.0 %**	**0.83 [0.60, 1.14]**
Total events: 16 (HBOT), 21 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.16 (P = 0.25)					
Test for subgroup differences: Not applicable					

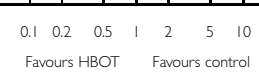
Analysis 6.2. Comparison 6 Local recurrence at two years, Outcome 2 Uterine cervix cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 6 Local recurrence at two years

Outcome: 2 Uterine cervix cancer

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 12 or fewer fractions in each group					
Watson 1978	17/36	31/35		38.6 %	0.53 [0.37, 0.77]
Subtotal (95% CI)	**36**	**35**		**38.6 %**	**0.53 [0.37, 0.77]**
Total events: 17 (HBOT), 31 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.37 (P = 0.00074)					
2 More than 12 fractions in each group					
Glassburn 1974	9/17	11/23		26.9 %	1.11 [0.60, 2.06]
Watson 1978	21/125	48/124		34.5 %	0.43 [0.28, 0.68]



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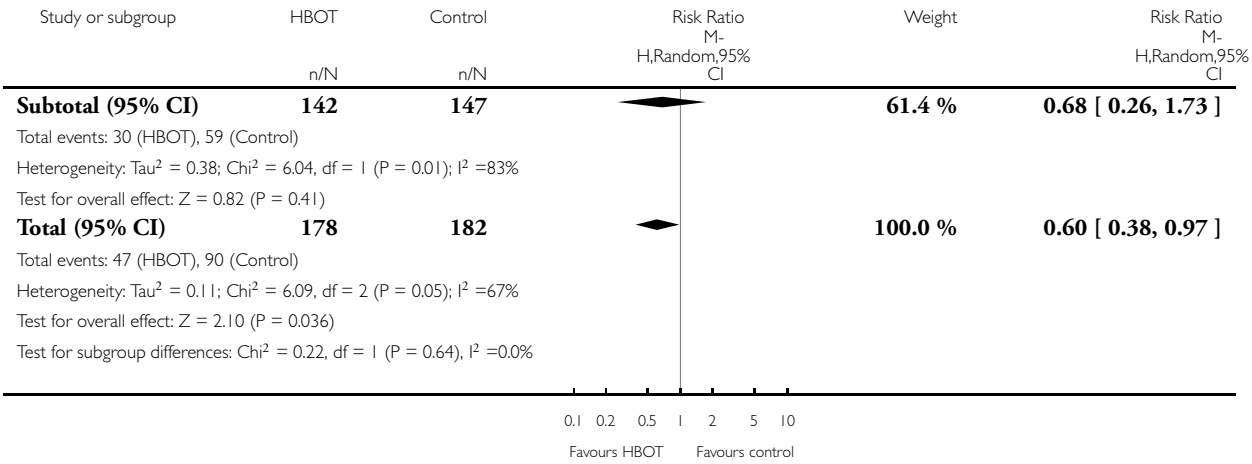
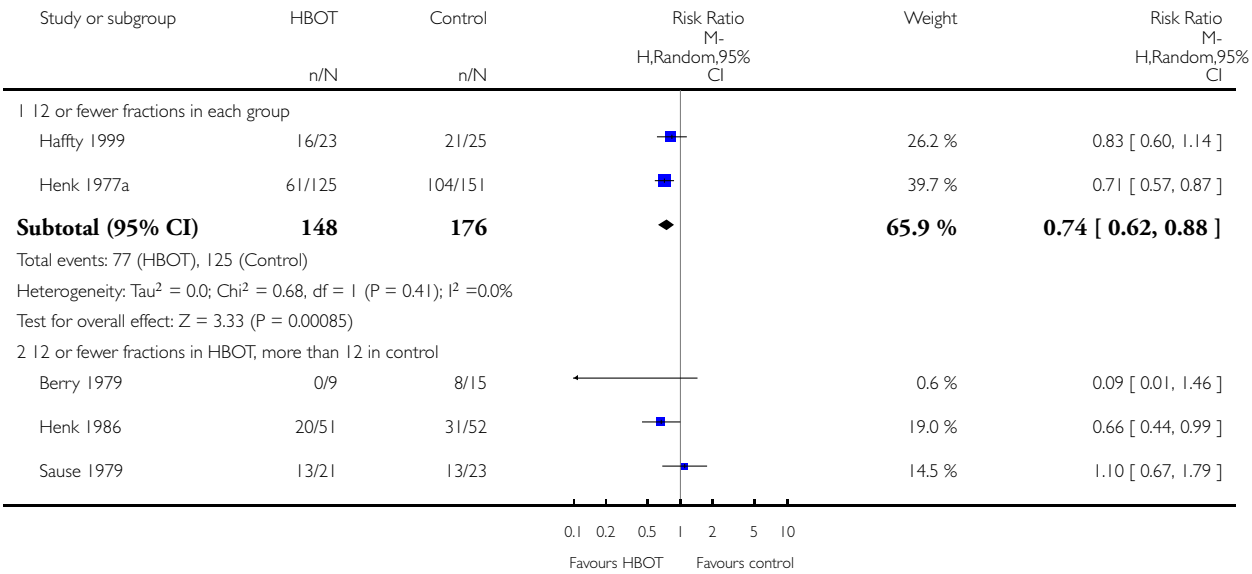


Analysis 7.1. Comparison 7 Local recurrence at five years, Outcome 1 Head and neck cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 7 Local recurrence at five years

Outcome: 1 Head and neck cancer



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Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**81**	**90**		**34.1 %**	**0.75 [0.39, 1.43]**
Total events: 33 (HBOT), 52 (Control)					
Heterogeneity: Tau^2 = 0.18; Chi^2 = 5.44, df = 2 (P = 0.07); I^2 =63%					
Test for overall effect: Z = 0.87 (P = 0.38)					
Total (95% CI)	**229**	**266**		**100.0 %**	**0.77 [0.62, 0.95]**
Total events: 110 (HBOT), 177 (Control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 5.90, df = 4 (P = 0.21); I^2 =32%					
Test for overall effect: Z = 2.46 (P = 0.014)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.97), I^2 =0.0%					

Analysis 7.2. Comparison 7 Local recurrence at five years, Outcome 2 Head and neck cancer - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 7 Local recurrence at five years

Outcome: 2 Head and neck cancer - best case scenario

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 12 or fewer fractions in each group					
Haffty 1999	16/23	21/25		26.5 %	0.83 [0.60, 1.14]
Henk 1977a	61/143	105/152		39.7 %	0.62 [0.50, 0.77]
Subtotal (95% CI)	**166**	**177**		**66.2 %**	**0.70 [0.52, 0.94]**
Total events: 77 (HBOT), 126 (Control)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 2.38, df = 1 (P = 0.12); I^2 =58%					
Test for overall effect: Z = 2.38 (P = 0.017)					
2 12 or fewer fractions in HBOT, more than 12 in control					
Berry 1979	0/9	8/15		0.6 %	0.09 [0.01, 1.46]
Henk 1986	20/52	31/52		18.9 %	0.65 [0.43, 0.97]

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Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Sause 1979	13/25	15/25		14.2 %	0.87 [0.53, 1.42]
Subtotal (95% CI)	**86**	**92**		**33.8 %**	**0.70 [0.43, 1.12]**
Total events: 33 (HBOT), 54 (Control)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 3.33$, df = 2 (P = 0.19); $I^2 = 40\%$					
Test for overall effect: Z = 1.49 (P = 0.14)					
Total (95% CI)	**252**	**269**		**100.0 %**	**0.70 [0.57, 0.86]**
Total events: 110 (HBOT), 180 (Control)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.67$, df = 4 (P = 0.23); $I^2 = 29\%$					
Test for overall effect: Z = 3.36 (P = 0.00078)					
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.99), $I^2 = 0.0\%$					

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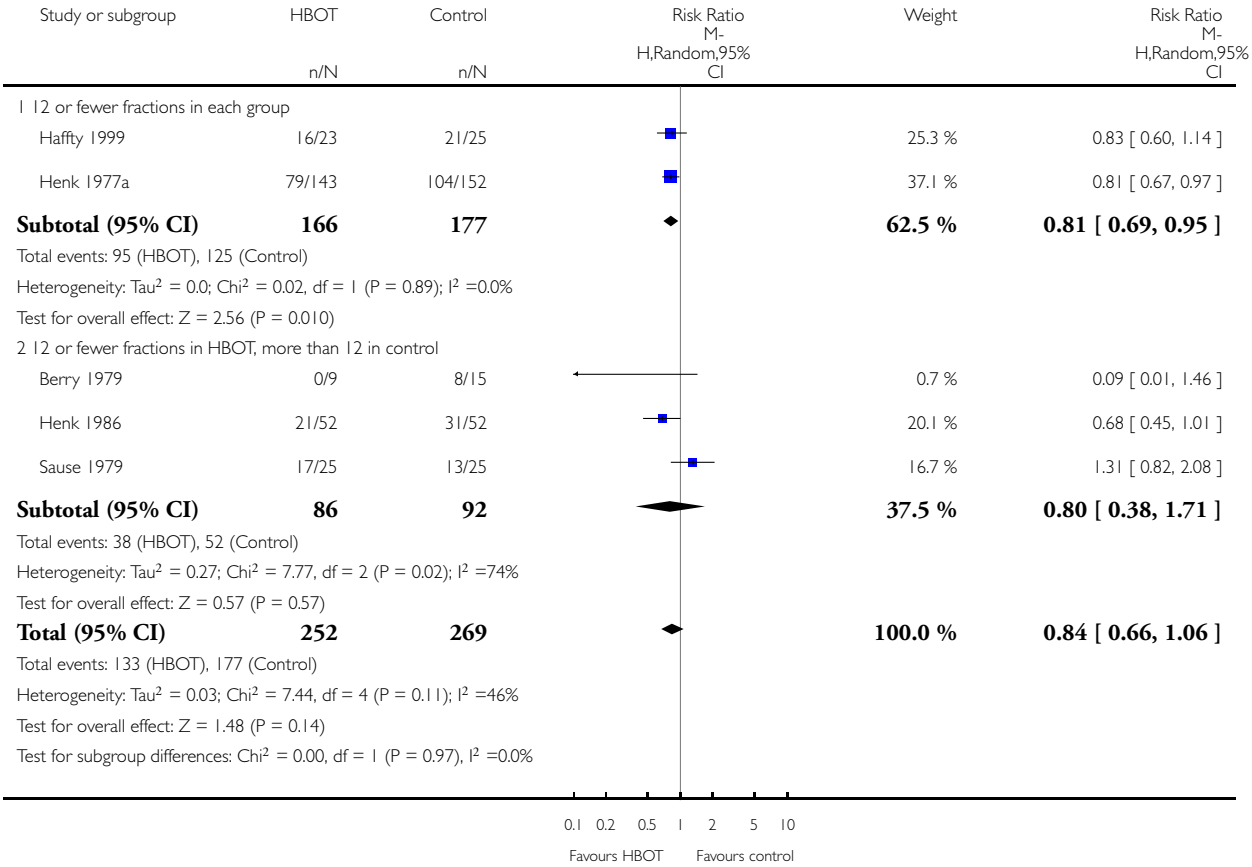
Analysis 7.3. Comparison 7 Local recurrence at five years, Outcome 3 Head and neck cancer - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 7 Local recurrence at five years

Outcome: 3 Head and neck cancer - worst case scenario



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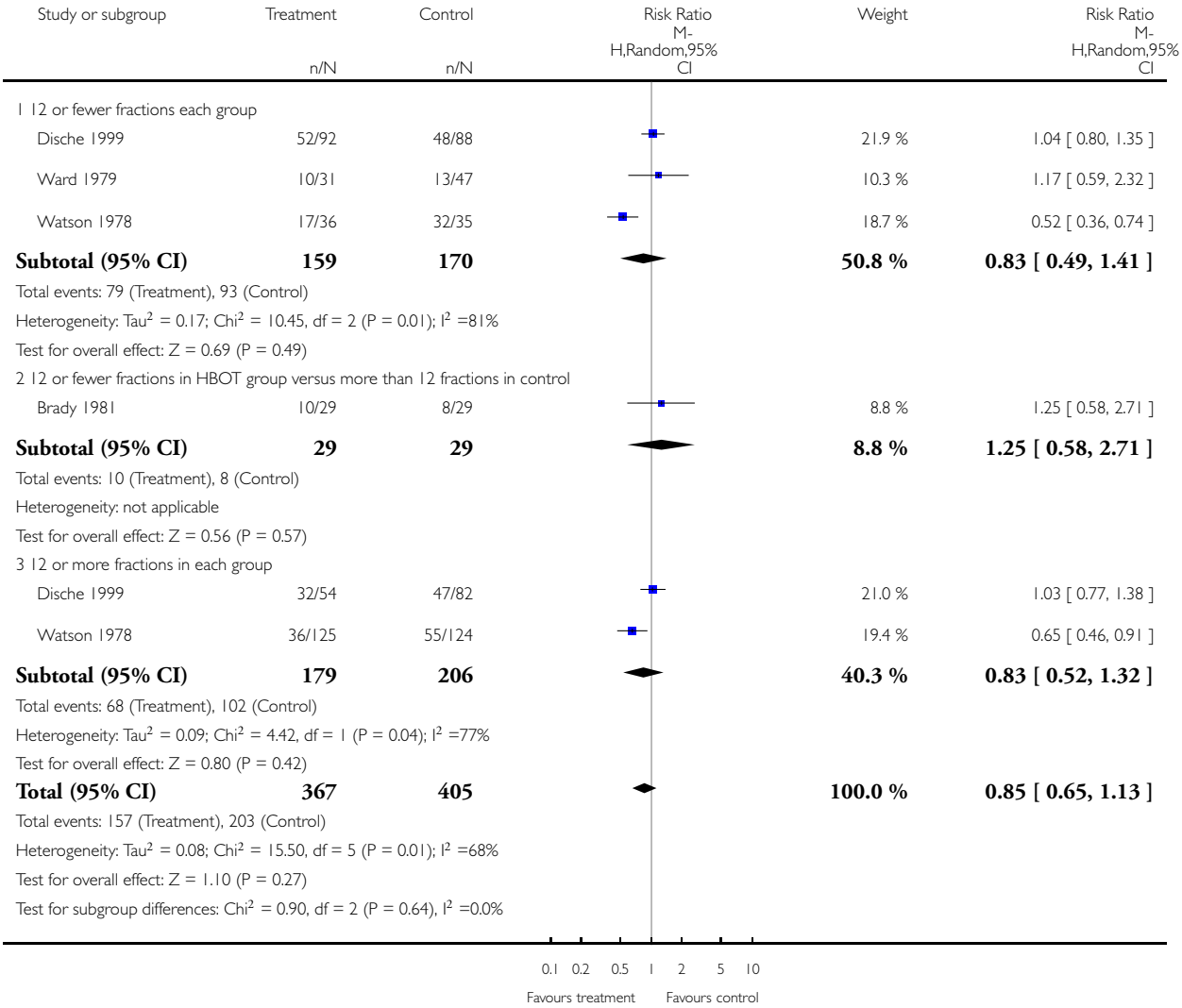
Analysis 7.4. Comparison 7 Local recurrence at five years, Outcome 4 Uterine cervix cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 7 Local recurrence at five years

Outcome: 4 Uterine cervix cancer



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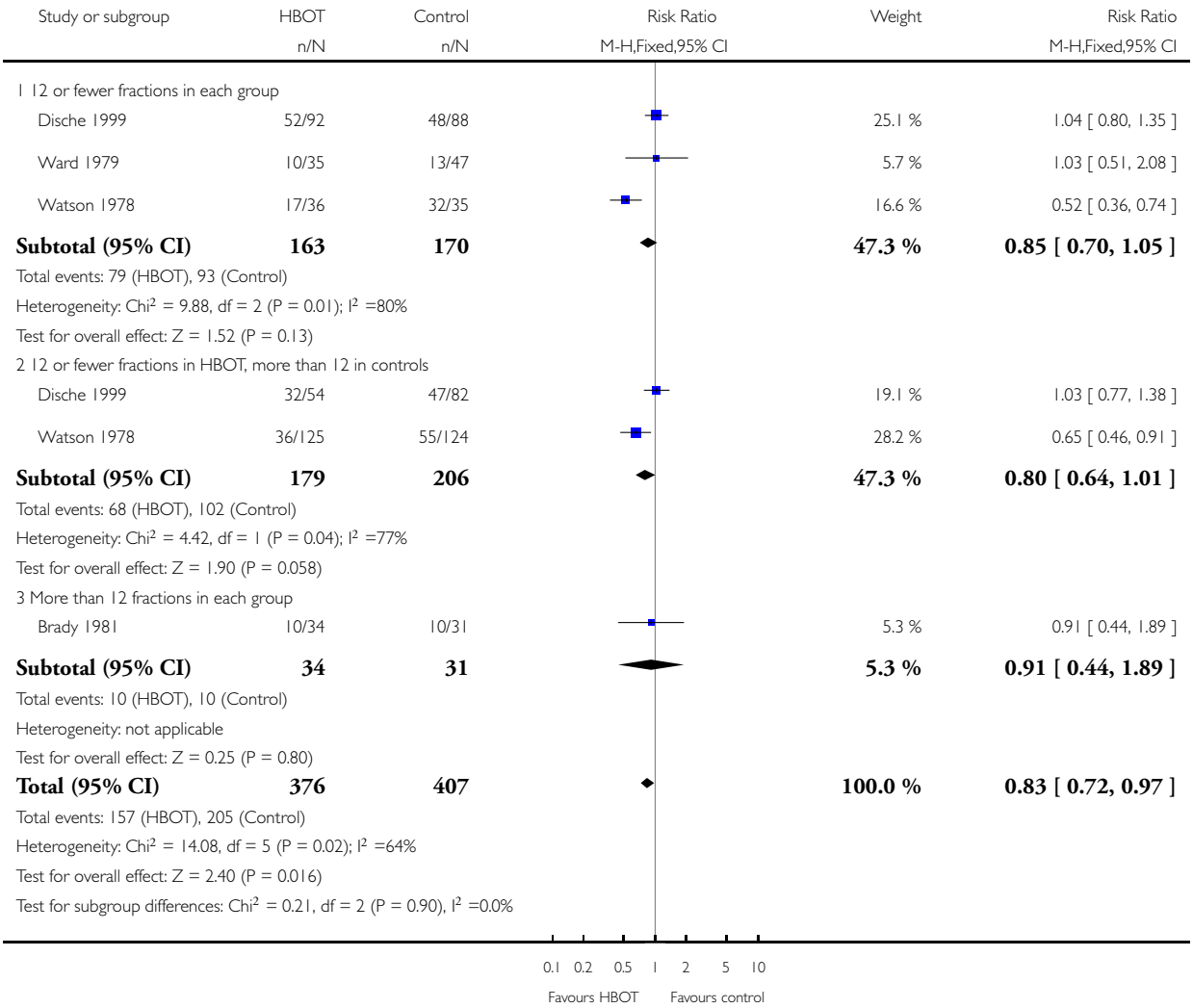
Analysis 7.5. Comparison 7 Local recurrence at five years, Outcome 5 Uterine cervix cancer - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 7 Local recurrence at five years

Outcome: 5 Uterine cervix cancer - best case scenario



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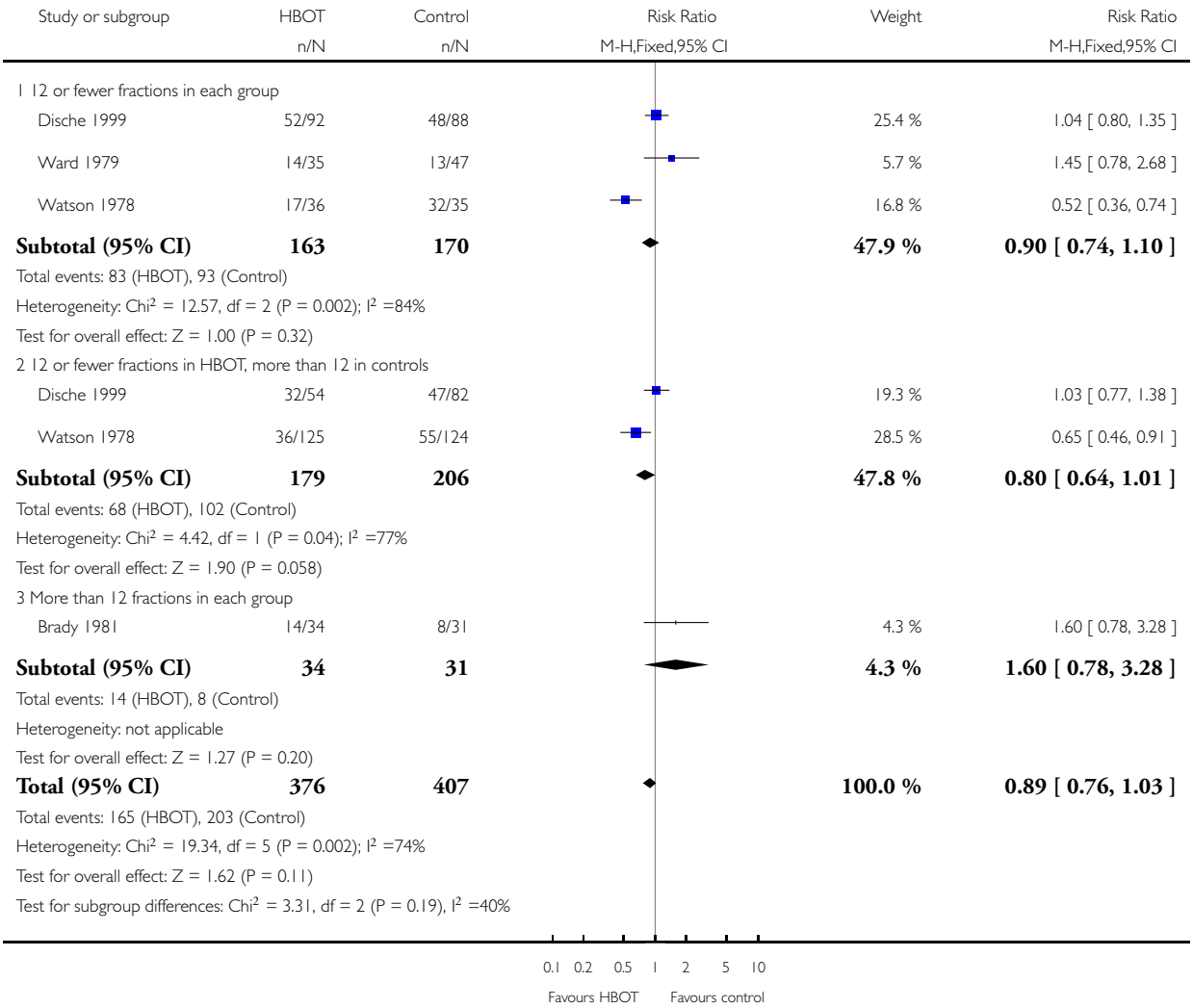
Analysis 7.6. Comparison 7 Local recurrence at five years, Outcome 6 Uterine cervix cancer - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 7 Local recurrence at five years

Outcome: 6 Uterine cervix cancer - worst case scenario



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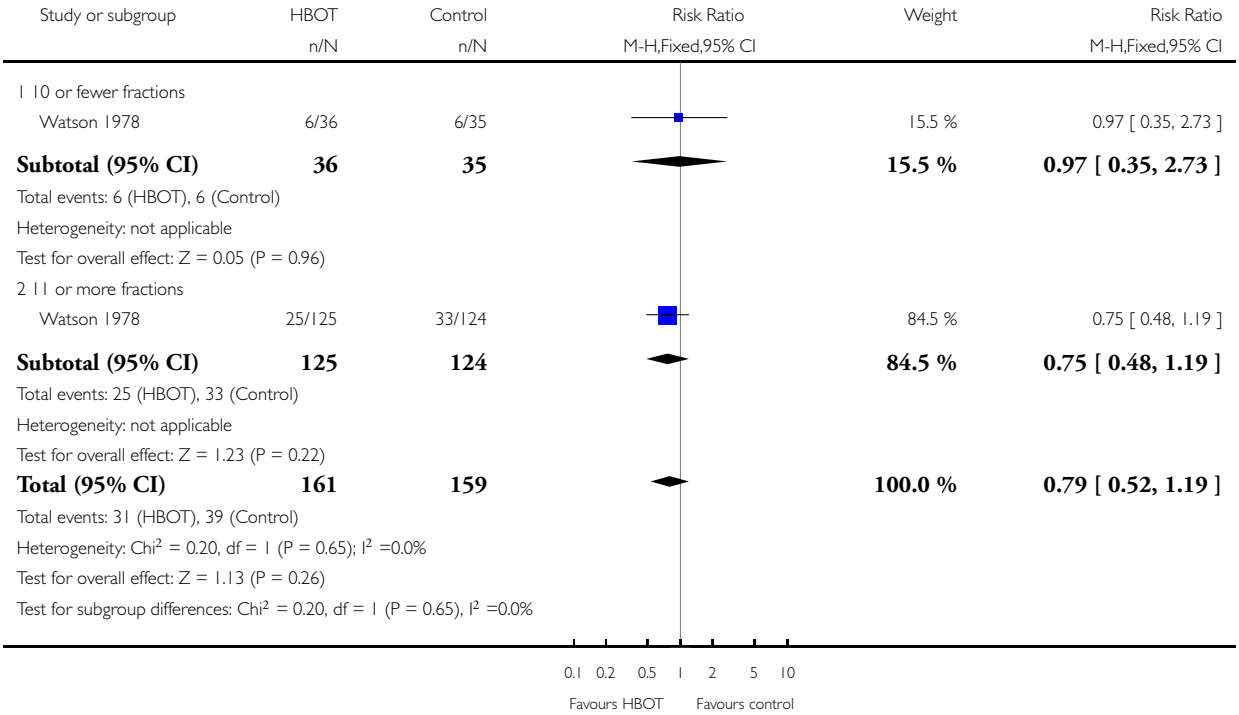
Analysis 8.1. Comparison 8 Metastases at one year, Outcome 1 Uterine cervix cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 8 Metastases at one year

Outcome: 1 Uterine cervix cancer



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Analysis 9.1. Comparison 9 Metastases at two years, Outcome 1 Uterine cervix cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 9 Metastases at two years

Outcome: 1 Uterine cervix cancer

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 More than 12 fractions in each group					
Fletcher 1977	18/109	18/124		19.9 %	1.14 [0.62, 2.07]
Glassburn 1974	4/17	3/23		3.0 %	1.80 [0.46, 7.02]
Watson 1978	65/125	65/124		77.1 %	0.99 [0.78, 1.26]
Total (95% CI)	**251**	**271**		**100.0 %**	**1.05 [0.84, 1.31]**
Total events: 87 (HBOT), 86 (Control)					
Heterogeneity: Chi^2 = 0.88, df = 2 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 0.39 (P = 0.70)					
Test for subgroup differences: Not applicable					

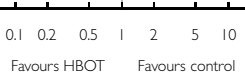
Analysis 9.2. Comparison 9 Metastases at two years, Outcome 2 Urinary bladder carcinoma.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 9 Metastases at two years

Outcome: 2 Urinary bladder carcinoma

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cade 1967	6/20	3/20		100.0 %	2.00 [0.58, 6.91]
Plenk 1972	0/19	0/21			Not estimable
Total (95% CI)	**39**	**41**		**100.0 %**	**2.00 [0.58, 6.91]**
Total events: 6 (HBOT), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					
Test for subgroup differences: Not applicable					



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Analysis 9.3. Comparison 9 Metastases at two years, Outcome 3 Carcinoma of the bronchus.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 9 Metastases at two years

Outcome: 3 Carcinoma of the bronchus

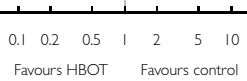
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cade 1967	13/25	12/24		100.0 %	1.04 [0.60, 1.80]
Total (95% CI)	**25**	**24**		**100.0 %**	**1.04 [0.60, 1.80]**

Total events: 13 (HBOT), 12 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable



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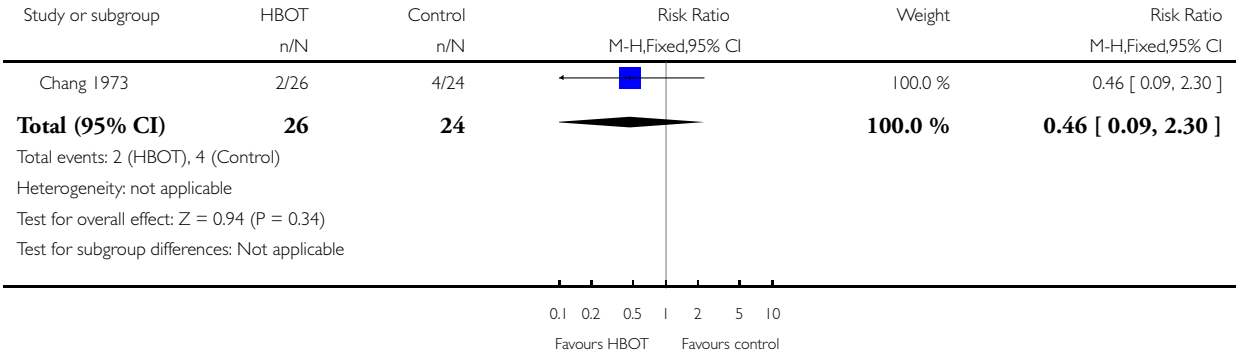
Analysis 10.1. Comparison 10 Metastases at five years, Outcome 1 Head and neck carcinoma.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 10 Metastases at five years

Outcome: 1 Head and neck carcinoma

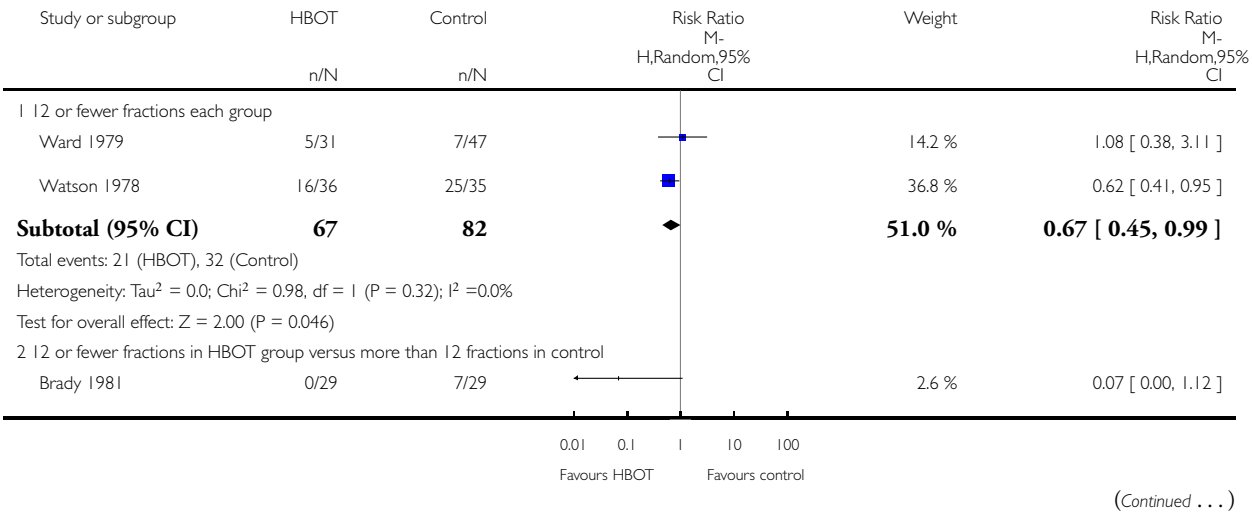


Analysis 10.2. Comparison 10 Metastases at five years, Outcome 2 Uterine cervix cancer.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 10 Metastases at five years

Outcome: 2 Uterine cervix cancer



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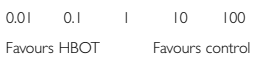
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**29**	**29**		**2.6 %**	**0.07 [0.00, 1.12]**
Total events: 0 (HBOT), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.88 (P = 0.060)					
3 More than 12 fractions in each group					
Watson 1978	65/125	65/124		46.4 %	0.99 [0.78, 1.26]
Subtotal (95% CI)	**125**	**124**		**46.4 %**	**0.99 [0.78, 1.26]**
Total events: 65 (HBOT), 65 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.07 (P = 0.95)					
Total (95% CI)	**221**	**235**		**100.0 %**	**0.79 [0.50, 1.26]**
Total events: 86 (HBOT), 104 (Control)					
Heterogeneity: Tau^2 = 0.11; Chi^2 = 7.17, df = 3 (P = 0.07); I^2 =58%					
Test for overall effect: Z = 1.00 (P = 0.32)					
Test for subgroup differences: Chi^2 = 6.03, df = 2 (P = 0.05), I^2 =67%					



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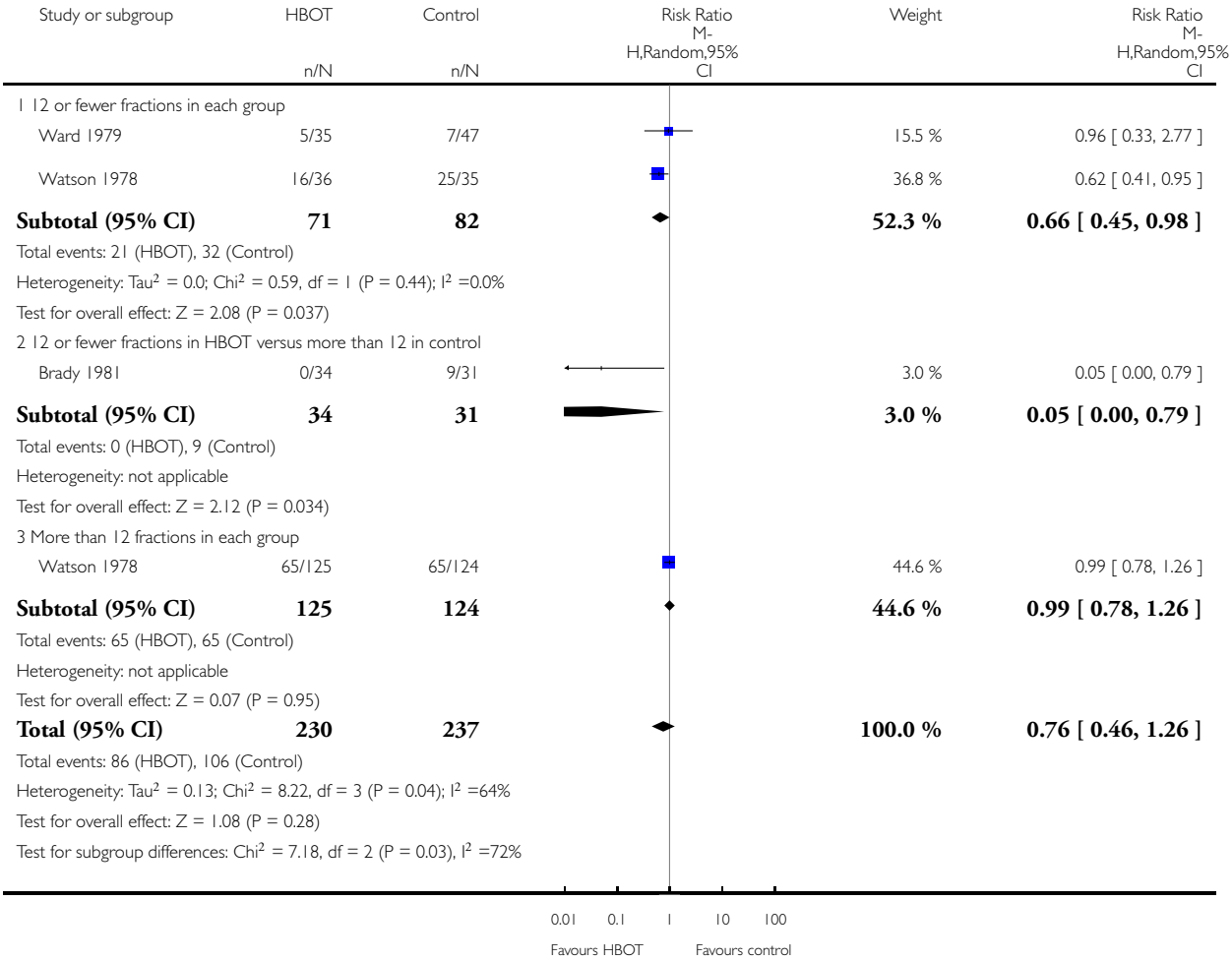
Analysis 10.3. Comparison 10 Metastases at five years, Outcome 3 Uterine cervix cancer - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 10 Metastases at five years

Outcome: 3 Uterine cervix cancer - best case scenario



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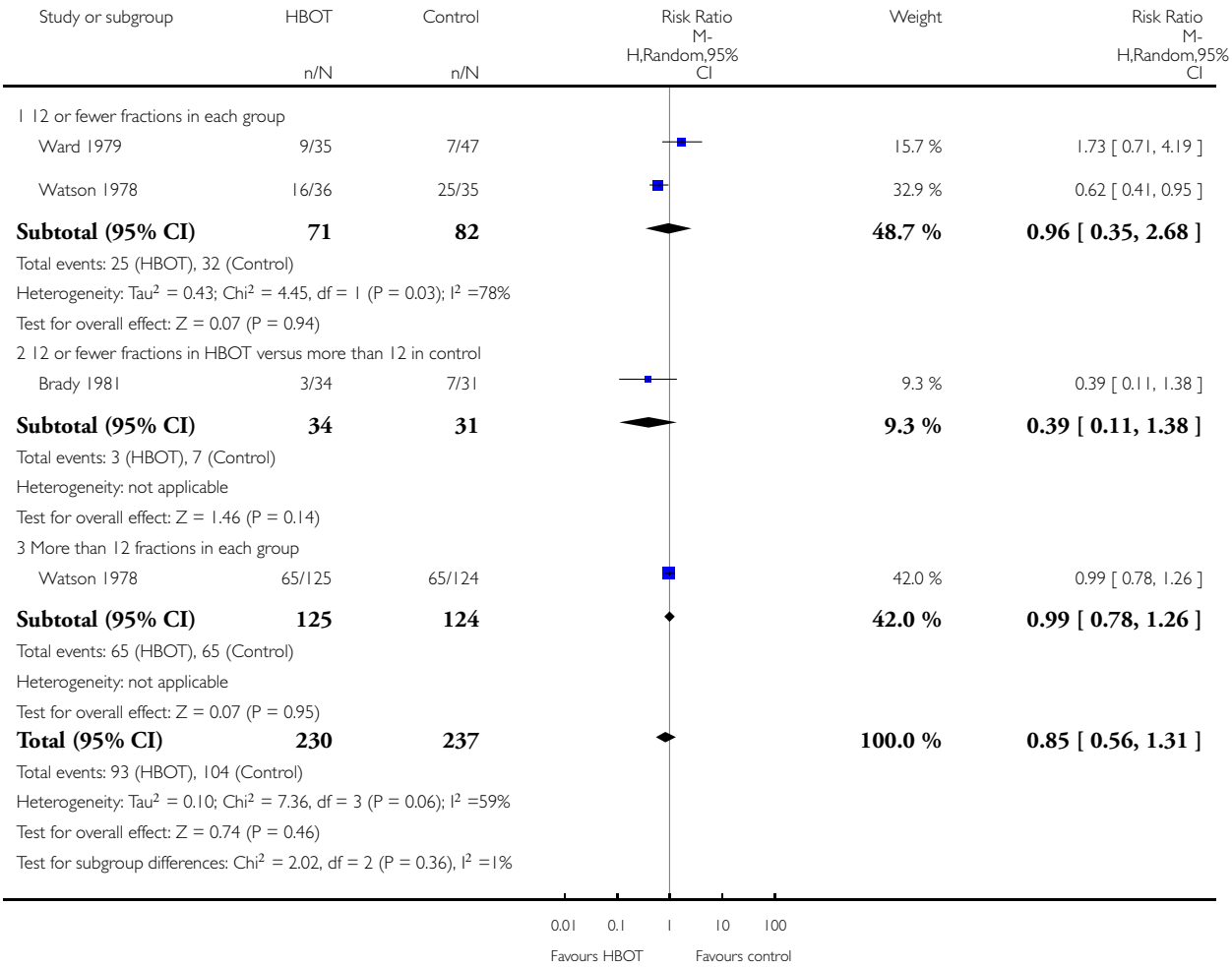
Analysis 10.4. Comparison 10 Metastases at five years, Outcome 4 Uterine cervix cancer - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 10 Metastases at five years

Outcome: 4 Uterine cervix cancer - worst case scenario



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Analysis 11.1. Comparison 11 Adverse events, Outcome 1 Death through radiation tissue injury.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 11 Adverse events

Outcome: 1 Death through radiation tissue injury

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dische 1999	15/146	12/167		73.6 %	1.43 [0.69, 2.95]
Watson 1978	9/161	4/159		26.4 %	2.22 [0.70, 7.07]
Total (95% CI)	**307**	**326**		**100.0 %**	**1.64 [0.89, 3.03]**

Total events: 24 (HBOT), 16 (Control)

Heterogeneity: Chi^2 = 0.40, df = 1 (P = 0.53); I^2 =0.0%

Test for overall effect: Z = 1.58 (P = 0.11)

Test for subgroup differences: Not applicable

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Analysis 11.2. Comparison 11 Adverse events, Outcome 2 Severe radiation tissue injury.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 11 Adverse events

Outcome: 2 Severe radiation tissue injury

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Brady 1981	7/29	7/29		19.4 %	1.00 [0.40, 2.49]
Haffty 1999	12/23	7/25		18.5 %	1.86 [0.89, 3.91]
Henk 1986	4/54	2/53		5.6 %	1.96 [0.38, 10.27]
Sause 1979	4/21	3/23		7.9 %	1.46 [0.37, 5.78]
Sealy 1986	27/60	7/64		18.7 %	4.11 [1.94, 8.74]
Ward 1979	8/31	6/47		13.2 %	2.02 [0.78, 5.26]
Watson 1978	20/161	6/159		16.7 %	3.29 [1.36, 7.98]
Total (95% CI)	**379**	**400**		**100.0 %**	**2.35 [1.66, 3.33]**

Total events: 82 (HBOT), 38 (Control)

Heterogeneity: $Chi^2 = 7.03$, df = 6 (P = 0.32); $I^2 = 15\%$

Test for overall effect: Z = 4.80 (P < 0.00001)

Test for subgroup differences: Not applicable

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Analysis 11.3. Comparison 11 Adverse events, Outcome 3 Severe radiation tissue injury - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 11 Adverse events

Outcome: 3 Severe radiation tissue injury - best case scenario

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Brady 1981	7/34	9/31		21.8 %	0.71 [0.30, 1.67]
Haffty 1999	12/23	7/25		15.5 %	1.86 [0.89, 3.91]
Henk 1986	4/55	2/53		4.7 %	1.93 [0.37, 10.08]
Sause 1979	4/25	5/25		11.6 %	0.80 [0.24, 2.64]
Sealy 1986	27/64	9/66		20.5 %	3.09 [1.58, 6.05]
Ward 1979	8/35	6/47		11.9 %	1.79 [0.68, 4.69]
Watson 1978	20/161	6/159		14.0 %	3.29 [1.36, 7.98]
Total (95% CI)	**397**	**406**		**100.0 %**	**1.94 [1.39, 2.69]**

Total events: 82 (HBOT), 44 (Control)

Heterogeneity: Chi^2 = 10.64, df = 6 (P = 0.10); I^2 =44%

Test for overall effect: Z = 3.94 (P = 0.000083)

Test for subgroup differences: Not applicable

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Analysis 11.4. Comparison 11 Adverse events, Outcome 4 Severe radiation tissue injury - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 11 Adverse events

Outcome: 4 Severe radiation tissue injury - worst case scenario

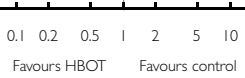
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Brady 1981	12/34	7/31		19.7 %	1.56 [0.71, 3.46]
Haffty 1999	12/23	7/25		18.1 %	1.86 [0.89, 3.91]
Henk 1986	5/55	2/53		5.5 %	2.41 [0.49, 11.88]
Sause 1979	8/25	3/25		8.1 %	2.67 [0.80, 8.90]
Sealy 1986	29/64	7/66		18.6 %	4.27 [2.02, 9.05]
Ward 1979	12/35	6/47		13.8 %	2.69 [1.12, 6.45]
Watson 1978	20/161	6/159		16.3 %	3.29 [1.36, 7.98]
Total (95% CI)	**397**	**406**		**100.0 %**	**2.69 [1.92, 3.77]**

Total events: 98 (HBOT), 38 (Control)

Heterogeneity: $Chi^2 = 4.42$, df = 6 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 5.76 (P < 0.00001)

Test for subgroup differences: Not applicable



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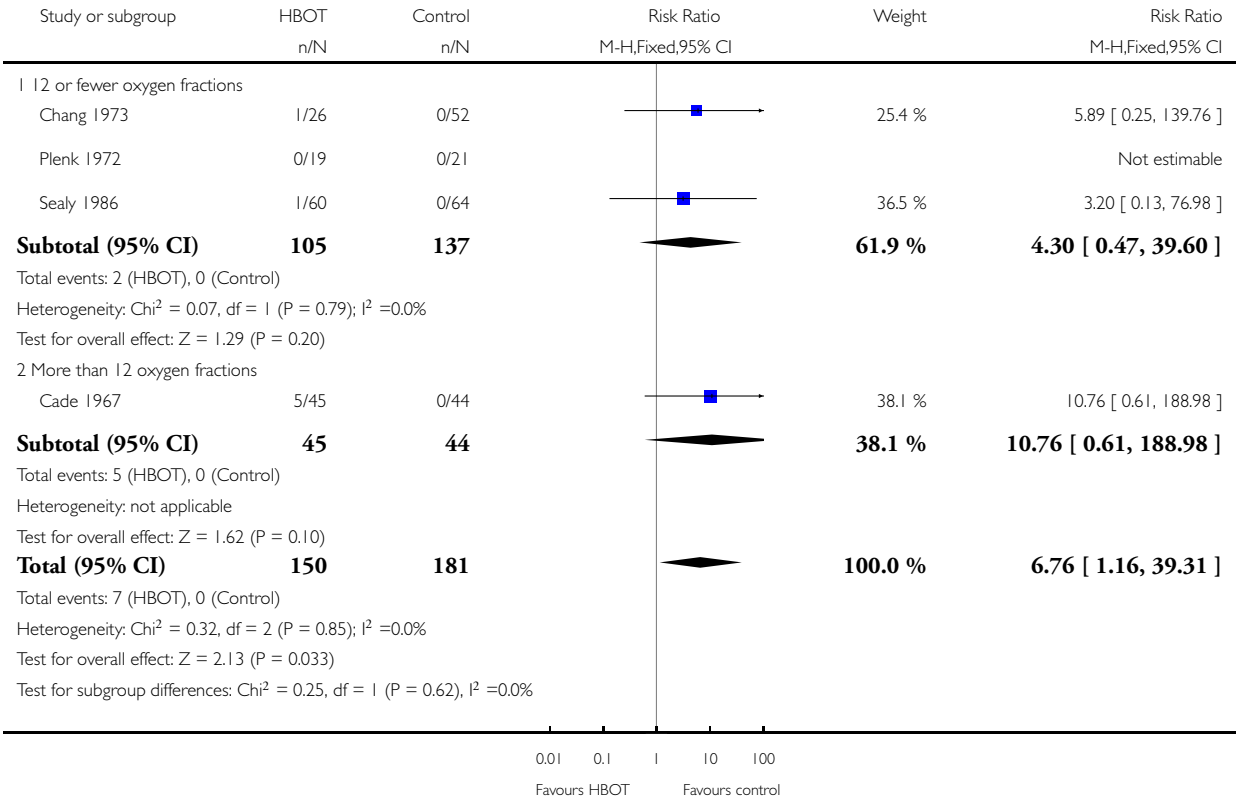
Analysis 11.5. Comparison 11 Adverse events, Outcome 5 Acute central nervous system oxygen toxicity.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 11 Adverse events

Outcome: 5 Acute central nervous system oxygen toxicity



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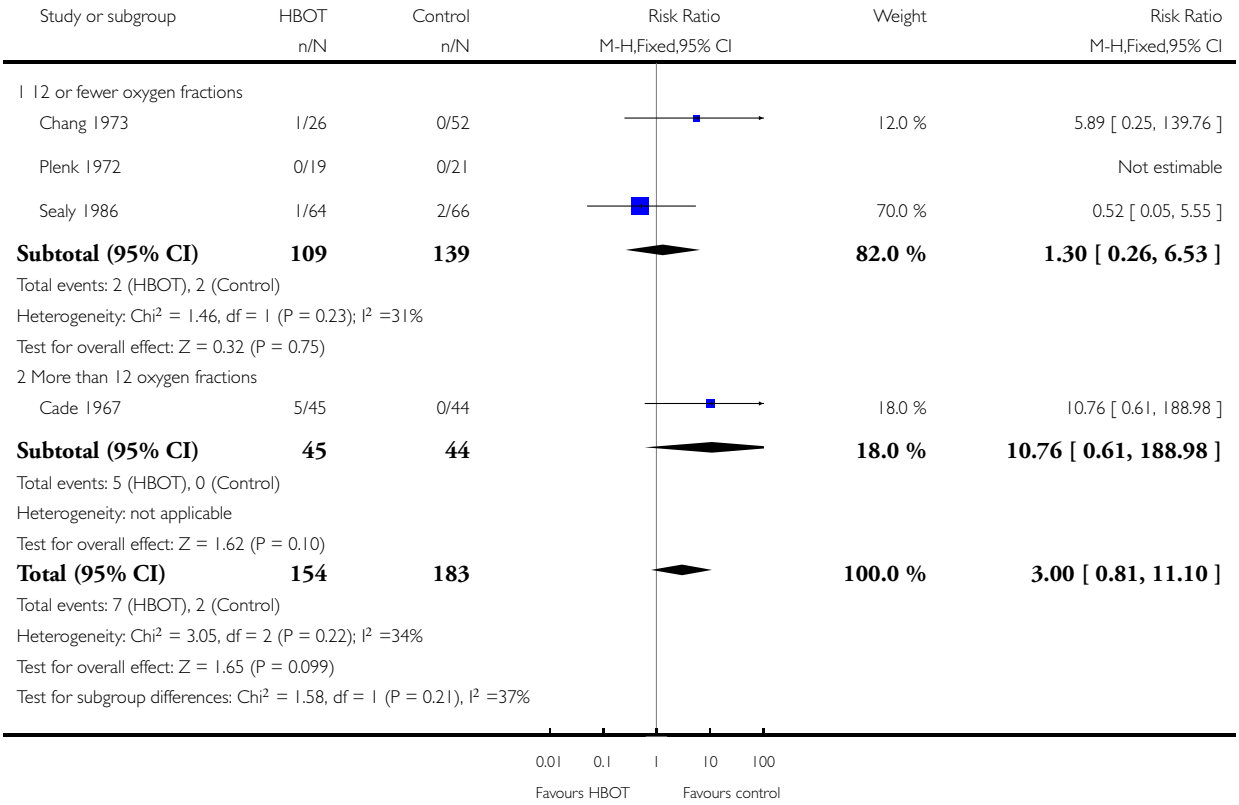
Analysis 11.6. Comparison 11 Adverse events, Outcome 6 Acute central nervous system toxicity - best case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 11 Adverse events

Outcome: 6 Acute central nervous system toxicity - best case scenario



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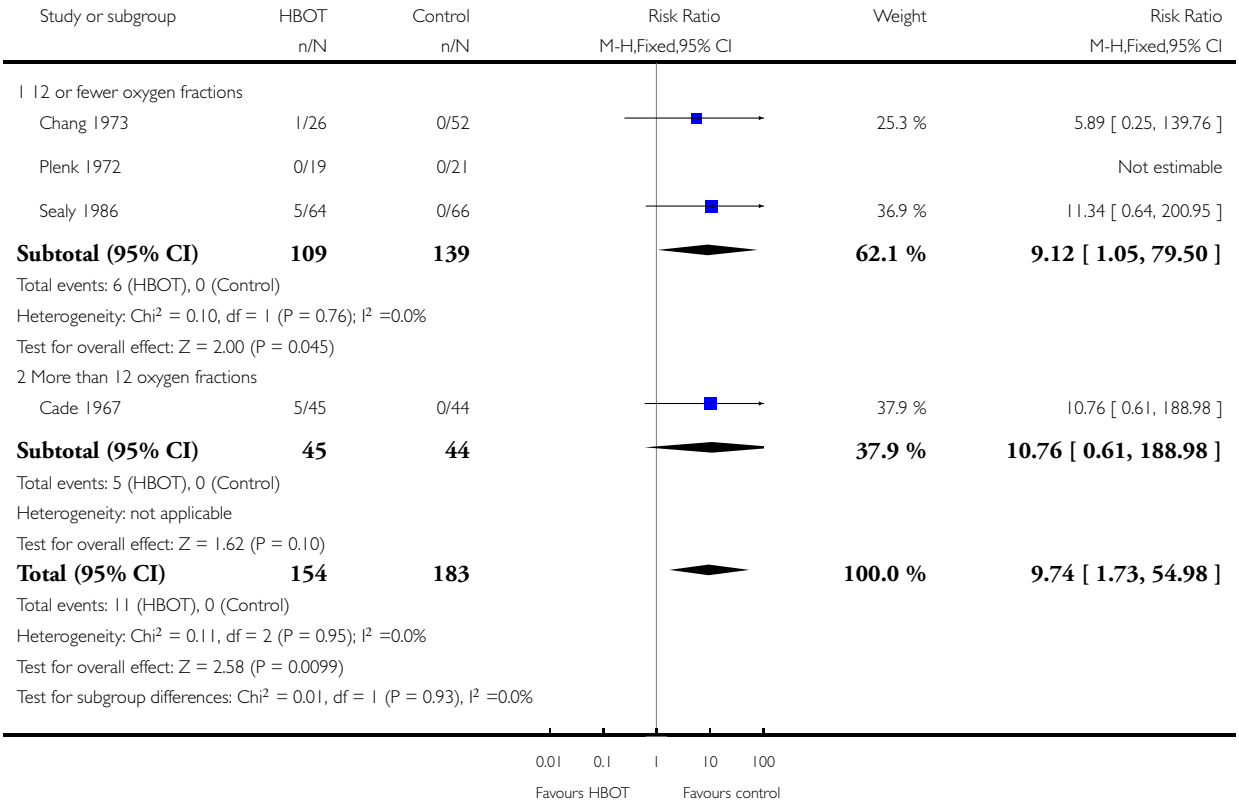
Analysis 11.7. Comparison 11 Adverse events, Outcome 7 Acute central nervous system toxicity - worst case scenario.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 11 Adverse events

Outcome: 7 Acute central nervous system toxicity - worst case scenario



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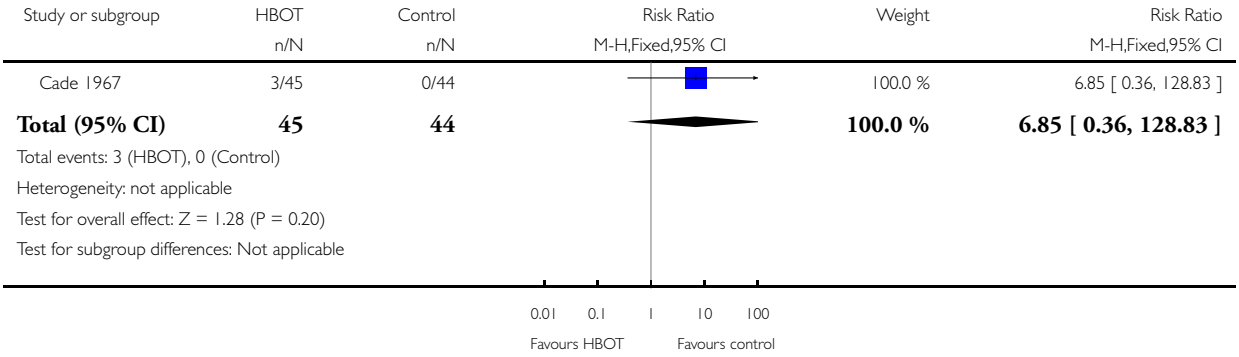
Analysis 11.8. Comparison 11 Adverse events, Outcome 8 Middle ear barotrauma.

Review: Hyperbaric oxygenation for tumour sensitisation to radiotherapy

Comparison: 11 Adverse events

Outcome: 8 Middle ear barotrauma



APPENDICES

Appendix 1. MEDLINE search strategy

1 Hyperbaric Oxygenation/
2 (hyperbaric and oxygen*).mp.
3 (hbo or hbot).mp.
4 (high adj3 (pressure or tension)).mp.
5 ((multiplace or monoplace) and chamber*).mp.
6 1 or 2 or 3 or 4 or 5
7 exp Radiotherapy/
8 radiotherap*.mp.
9 radiation.mp.
10 irradiat*.mp.
11 radiotherapy.fs.
12 7 or 8 or 9 or 10 or 11
13 randomized controlled trial.pt.
14 controlled clinical trial.pt.
15 randomized.ab.
16 placebo.ab.
17 clinical trials as topic.sh.-
18 randomly.ab.
19 trial.ti.
20 13 or 14 or 15 or 16 or 17 or 18 or 19
21 6 and 12 and 20
key:

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mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier
pt=publication type
ab=abstract
sh=subject heading
ti=title

Appendix 2. EMBASE search strategy

1 hyperbaric oxygen/
2 (hyperbaric and oxygen*).mp.
3 (hbo or hbot).mp.
4 (high adj3 (pressure or tension)).mp.
5 ((multiplace or monoplace) and chamber*).mp.
6 1 or 2 or 3 or 4 or 5
7 cancer radiotherapy/
8 exp radiotherapy/
9 radiotherap*.mp.
10 radiation.mp.
11 irradiat*.mp.
12 rt.fs.
13 7 or 8 or 9 or 10 or 11 or 12
14 crossover procedure/
15 randomized controlled trial/
16 single blind procedure/
17 random*.mp.
18 factorial*.mp.
19 (crossover* or cross over* or cross-over*).mp.
20 placebo*.mp.
21 (doubl* adj blind*).mp.
22 (singl* adj blind*).mp.
23 assign*.mp.
24 allocat*.mp.
25 volunteer*.mp.
26 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27 6 and 13 and 26
key:
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer

Appendix 3. CINAHL search strategy

1. exp Radiotherapy/
2. exp brachytherapy/.
3. exp radiation-sensitising agents/
4. (radiation or radiother*).mp.
5. 1 or 2 or 3 or 4
6. exp HYPERBARIC OXYGENATION/
7. (high adj5 (pressur$ or oxygen$)).mp.
8. hyperbaric$.mp.
9. 6 or 7 or 8
10. oxygen$.mp.
11. 9 and 10

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12. (HBO or HBOT).mp.
13. multiplace chamber$.mp.
14. monoplace chamber*.mp.
15. 11 or 12 or 13 or 14
16. 5 and 15
17. (random$ or controlled clinical trial or groups).mp.
18. 16 and 17

Appendix 4. CENTRAL search strategy

#1 MeSH descriptor Hyperbaric Oxygenation, this term only
#2 hyperbaric and oxygen*
#3 hbo and hbot
#4 high near/3 (pressure or tension)
#5 (multiplace or monoplace) and chamber*
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Radiotherapy explode all trees
#8 radiotherap*
#9 radiation
#10 irradiat*
#11 Any MeSH descriptor with qualifier: RT
#12 (#7 OR #8 OR #9 OR #10 OR #11)
#13 (#6 AND #12)

WHAT'S NEW

Last assessed as up-to-date: 6 January 2012.

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 4, 2005

Date	Event	Description
11 February 2015	Amended	Contact details updated.
27 March 2014	Amended	Contact details updated.

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(*Continued*)

21 February 2012	New citation required but conclusions have not changed	New searches executed March 2011 but no new studies identified
6 January 2012	New search has been performed	Text updated and study flow diagram added.
4 October 2008	New search has been performed	Review updated, no new trials identified when searches were re-run on 27 September 2008
30 April 2008	Amended	Converted to new review format.
16 July 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Michael Bennett: Principal author, conception, search strategy and execution, data extraction and critical appraisal, Hyperbaric Medicine content expert, statistical analysis.

Robert Smee: Co-author, data extraction and critical appraisal, Radiation Oncology content expert.

John Feldmeier: Co-author, Radiation Oncology and Hyperbaric Medicine content expert.

Chris Milross: Co-author Background and Discussion, Radiation Oncology content expert.

DECLARATIONS 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).

SOURCES OF SUPPORT

Internal sources

- No specific support provided, Australia.

External sources

- No sources of support, Not specified.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Radiation Tolerance; Bronchial Neoplasms [mortality; radiotherapy]; Combined Modality Therapy [methods]; Esophageal Neoplasms [mortality; radiotherapy]; Head and Neck Neoplasms [mortality; radiotherapy]; Hyperbaric Oxygenation [adverse effects; *methods]; Neoplasm Recurrence, Local [epidemiology]; Neoplasms [mortality; *radiotherapy]; Randomized Controlled Trials as Topic; Rectal Neoplasms [mortality; radiotherapy]; Time Factors; Urinary Bladder Neoplasms [mortality; radiotherapy]; Uterine Cervical Neoplasms [mortality; radiotherapy]

MeSH check words

Female; Humans; Male

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