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Hyperbaric oxygen therapy for late radiation tissue injury (Review)

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[Intervention Review]

Hyperbaric oxygen therapy for late radiation tissue injury

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ABSTRACT

Background

Cancer is a significant global health problem. Radiotherapy is a treatment for many cancers and about 50% of people having radiotherapy will be long-term survivors. Some will experience late radiation tissue injury (LRTI) developing months or years later. Hyperbaric oxygen therapy (HBOT) has been suggested as a treatment for LRTI based upon the ability to improve the blood supply to these tissues. It is postulated that HBOT may result in both healing of tissues and the prevention of problems following surgery.

Objectives

To assess the benefits and harms of HBOT for treating or preventing LRTI.

Search methods

We updated the searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 11), MEDLINE, EMBASE, DORCTIHM and reference lists of articles in December 2015. We also searched for ongoing trials at clinicaltrials.gov.

Selection criteria

Randomised controlled trials (RCTs) comparing the effect of HBOT versus no HBOT on LRTI prevention or healing.

Data collection and analysis

Three review authors independently evaluated the quality of the relevant trials using the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* and extracted the data from the included trials.

Main results

Fourteen trials contributed to this review (753 participants). There was some moderate quality evidence that HBOT was more likely to achieve mucosal coverage with osteoradionecrosis (ORN) (risk ratio (RR) 1.3; 95% confidence interval (CI) 1.1 to 1.6, P value = 0.003, number needed to treat for an additional beneficial outcome (NNTB) 5; 246 participants, 3 studies). There was also moderate quality evidence of a significantly improved chance of wound breakdown without HBOT following operative treatment for ORN (RR 4.2; 95% CI 1.1 to 16.8, P value = 0.04, NNTB 4; 264 participants, 2 studies). From single studies there was a significantly increased chance of improvement or cure following HBOT for radiation proctitis (RR 1.72; 95% CI 1.0 to 2.9, P value = 0.04, NNTB 5), and following both surgical flaps (RR 8.7; 95% CI 2.7 to 27.5, P value = 0.0002, NNTB 4) and hemimandibulectomy (RR 1.4; 95% CI 1.1 to 1.8, P value = 0.001, NNTB 5). There was also a significantly improved probability of healing irradiated tooth sockets following dental extraction (RR 1.4; 95% CI 1.1 to 1.7, P value = 0.009, NNTB 4).

There was no evidence of benefit in clinical outcomes with established radiation injury to neural tissue, and no randomised data reported on the use of HBOT to treat other manifestations of LRTI. These trials did not report adverse events.

Authors' conclusions

These small trials suggest that for people with LRTI affecting tissues of the head, neck, anus and rectum, HBOT is associated with improved outcome. HBOT also appears to reduce the chance of ORN following tooth extraction in an irradiated field. There was no such evidence of any important clinical effect on neurological tissues. The application of HBOT to selected participants and tissues may be justified. Further research is required to establish the optimum participant selection and timing of any therapy. An economic evaluation should be undertaken.

PLAIN LANGUAGE SUMMARY

Hyperbaric oxygen therapy for the treatment of the late effects of radiotherapy

The issue
There is a risk of serious complications developing after radiation treatment (radiotherapy) for cancer (late radiation tissue injury (LRTI)). These problems can be very difficult to resolve and there is some doubt as to the best approaches to treatment. Hyperbaric oxygen therapy (HBOT) involves breathing oxygen in a specially designed chamber. It is used as a treatment to improve oxygen supply to damaged tissue (cells within the body) and support healing.

The aim of the review
We searched medical databases for clinical studies aimed to find the evidence for or against the ability of HBOT, compared to either no treatment or alternative treatments, to improve these complications. The evidence was current to December 2015.

What were the main findings?
There was some evidence that HBOT improved outcome in LRTI affecting bone and soft tissues of the head and neck, for radiation proctitis (inflammation of the lower part of the large intestine caused by radiotherapy treatment) and to prevent the development of osteoradionecrosis (bone death caused by radiotherapy treatment) following tooth extraction in an irradiated field. There was no such evidence of any important clinical effect on tissues in the nervous system.

Quality of the evidence
The evidence was generally of moderate quality and limited by small numbers of participants, poor reporting of methods and results, and uncertainty as to the exact degree of improvement with HBOT.

What are the conclusions?
The application of HBOT to selected participants and tissues may be justified. Studies of radiation injury suggest that other tissues are also likely to respond (e.g. bladder). Further research is required to establish which people may respond and the best timing of such therapy. A study of costs would also be useful.

Summary of findings for the main comparison. Hyperbaric oxygen therapy versus standard approach for people with osteoradionecrosis

Hyperbaric oxygen therapy versus standard approach for people with osteoradionecrosis

Patient or population: late radiation tissue injury
Setting: hospital
Intervention: hyperbaric oxygen therapy
Comparison: standard treatment options

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard treatment options	Risk with hyperbaric oxygen therapy				
Complete mucosal cover in people with osteoradionecrosis (mucosal cover) assessed with: physical examination follow-up: 12-18 months	Study population		RR 1.30 (1.09 to 1.55)	246 (3 RCTs)	⊕⊕⊕⊖ Moderate[1]	1 trial enrolled people with relatively milder disease and 2 trials enrolled people with advanced disease
	651 per 1000	846 per 1000 (709 to 1000)				
	Low					
	250 per 1000	325 per 1000 (273 to 388)				
	High					
	900 per 1000	1000 per 1000 (981 to 1000)				
Wound dehiscence following complex head and neck surgery (wound healing) assessed with: clinical examination follow-up: 3 months	Study population		RR 4.23 (1.06 to 16.83)	264 (2 RCTs)	⊕⊕⊕⊖ Moderate[2]	Relatively short-term outcome
	280 per 1000	1000 per 1000 (297 to 1000)				
	Low					
	100 per 1000	423 per 1000 (106 to 1000)				
	High					

	500 per 1000	1000 per 1000 (530 to 1000)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] High risk of bias in some areas due to poor reporting.
[2] Imprecision in estimate.

BACKGROUND

Description of the condition

Cancer is a significant global health problem. According to World Health Organization (WHO) statistics, in 2012 more than 14 million people were diagnosed with cancer, and cancer caused more than eight million deaths the same year (IARC 2013). Radiotherapy is a well-established treatment of suitable malignancies in a wide variety of anatomical areas. Of the approximately 1.2 million new cases of invasive cancer diagnosed annually in the USA, for example, about 50% will receive radiotherapy (Jemal 2002), and of these about 50% will be long-term survivors. While radiotherapy may acutely injure any normal tissue in the path of the radiation, this acute injury generally heals spontaneously following completion of the treatment course. Serious radiation-related complications developing months or years after radiation treatment, collectively known as late radiation tissue injury (LRTI), are relatively rare and will affect between 5% and 15% of those long-term survivors who received radiotherapy, although the incidence varies widely with dose, age and site (Flannigan 2014; Stone 2003; Thompson 1999; Waddell 1999). Although any tissue may be affected, LRTI is in practice most common in the head and neck, chest wall, breast and pelvis - reflecting the anatomical areas most commonly irradiated and the likelihood of survival for people treated for cancer at these anatomical sites.

When LRTIs occur, tissues undergo a progressive deterioration characterised by a reduction in the density of small blood vessels (reduced vascularity) and the replacement of normal tissue cells with dense fibrous tissue (fibrosis), until there is insufficient oxygen supplied to sustain normal function. This situation is frequently exacerbated by secondary damage due to infection or surgery in the affected area (Rubin 1984). This progressive and delayed radiation damage may reach a critical point where the tissue breaks down to form an ulcer or area of cell death (radiation necrosis or radionecrosis). LRTI can affect any organ system, although some tissues are more sensitive to radiation effects than others (Thompson 1999; Trott 1984; Waddell 1999).

Historically, the management of these injuries has been unsatisfactory. LRTI may be life threatening and may significantly reduce quality of life (QoL). Conservative treatment is usually restricted to symptom management, while definitive treatment traditionally entails surgery to remove the affected part and extensive repair (Stone 2003). Surgical intervention in an irradiated field is often disfiguring and associated with an increased incidence of delayed healing, breakdown of a surgical wound or infection. Hyperbaric oxygen therapy (HBOT) has been widely reported to improve LRTI in a wide range of tissues (Feldmeier 2002; Hampson 2012).

Description of the intervention

HBOT has been proposed to improve tissue quality, promote healing and prevent breakdown of irradiated tissue fields. It may be defined as the therapeutic administration of 100% oxygen at environmental pressures greater than 1 atmosphere absolute (ATA). Administration involves placing the person in an airtight vessel, increasing the pressure within that vessel, and giving 100% oxygen for respiration. In this way, it is possible to deliver a greatly increased partial pressure of oxygen to the lungs, blood and tissues. Typically, treatments involve pressurisation to between 2.0 and 2.5 ATA for periods between 60 and 120 minutes once or twice daily to a total of 30 to 60 sessions of treatment.

How the intervention might work

The intermittent application of HBOT is the only intervention that has been shown to increase the number of blood vessels in irradiated tissue. This has been demonstrated by Marx in a rabbit mandibular (jaw bone) model and further confirmed by serial tissue oxygen level measurements using electrodes placed on the overlying skin (transcutaneous oximetry ($PtcO_2$)) in humans undergoing a course of therapy for radiation necrosis of the mandible (Marx 1988; Marx 1990). In the rabbit study, the jaw and surrounding soft tissues were heavily irradiated and one group 'rescued' with HBOT six months later. The two control groups showed no improvement while a series of 20 sessions at 2.4 ATA on 100% oxygen returned the density of blood vessels to 80% of normal. In the human study, a progressive recovery of low $PtcO_2$ readings into the normal range was achieved in a group of people receiving therapy for underlying osteoradionecrosis (ORN) (radiation necrosis of bone).

HBOT seems most likely to achieve such improvements through a complex series of changes in affected tissues. Tissue swelling is probably improved through an osmotic effect of oxygen, while the establishment of a steep oxygen gradient across an irradiated tissue margin is a powerful stimulus to the growth of new blood vessels (Davis 1988; Hills 1999). In addition, improving oxygen levels will improve white cell and fibroblast function, further enhancing wound healing (Mandell 1974). Improved tissue quality has been demonstrated in a model of radiation small bowel injury (Feldmeier 1995; Feldmeier 1998).

Why it is important to do this review

While HBOT has been used for LRTI since at least 1975 (Mainous 1975), most clinical studies have been limited to relatively small case series or individual case reports. There have been relatively few comparative studies published, and no previous quantitative systematic reviews of which we are aware. In one semi-quantitative review, Feldmeier and Hampson located 71 such reports involving 1193 participants across eight different tissues (Feldmeier 2002). In these participants, for whom conservative treatment had failed to improve symptoms, there were clinically significant improvements in the majority of people. Results varied between tissue types, with neurological tissue appearing the most resistant to improvement. Only 7 of 71 reports indicated a generally poor response to HBOT. More recently, Hoggan 2014 systematically reviewed the literature and found 11 studies of HBOT for LRTI, concluding there was support for the use of HBOT in selected tissues. The present review complements Feldmeier 2002 and Hoggan 2014 by using explicit Cochrane methodology to locate, quantitatively appraise and summarise the comparative data, while not discussing in any detail the non-comparative series summarised in those reviews.

HBOT is associated with some risk of adverse events including damage to the ears, sinuses and lungs from the effects of pressure; temporary worsening of short sightedness (myopia); claustrophobia and oxygen poisoning. Although serious adverse events are rare, HBOT cannot be regarded as an entirely benign intervention. It has further been suggested that HBOT may increase the incidence and rate, or both, of growth of tumours in people with

a history of malignancy. One comprehensive review did not support these concerns (Feldmeier 2003).

OBJECTIVES

To assess the benefits and harms of HBOT for treating or preventing LRTI

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and pseudo-RCTs that compared the effect of a regimen including HBOT on any form of LRTI, with any treatment regimen not including HBOT.

Types of participants

Any person with LRTI (including necrosis) of whatever tissue. We also accepted people treated with large-dose radiotherapy likely to induce relatively early necrosis (e.g. radiosurgery to a brain lesion).

Types of interventions

We accepted trials comparing regimens that included HBOT with similar regimens that excluded HBOT. Where co-interventions differed significantly between studies, we clearly stated this and discussed the implications.

The intervention under examination was HBOT administered in a compression chamber between pressures of 1.5 and 4.0 ATA and treatment times between 30 and 120 minutes daily or twice daily. These parameters excluded trivial treatments and highly toxic exposures. The comparator groups were diverse, and we accepted any standard treatment regimen designed to promote tissue healing or prevent further deterioration.

Types of outcome measures

Appropriate outcome measure depended on the nature of the LRTI and the anatomical location. Studies were eligible for inclusion if they reported any of the following outcome measures.

All anatomical areas

Primary outcomes

1. Survival.
2. Complete resolution of necrosis or tissue damage.
3. Complete resolution or substantial improvement of necrosis or tissue damage.
4. Improvement in LENT-SOMA (Late Effects Normal Tissues - Subjective, Objective, Management, Analytic) scale

(The European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) jointly developed the LENT-SOMA scales in 1995 to standardise assessment of LRTI (Pavy 1995). Scales are location specific and are summarised in a number of forms for each location. We discussed the implications for pooling as required. Table 1 shows the scale dimensions.)

Secondary outcomes

1. Resolution of pain.
2. Resolution of swelling.
3. Improvement in QoL, function or both (we will consider any measures of these outcomes, both general and organ specific, e.g. SF46 or bowel bother scale).

Osteoradionecrosis

Primary outcomes

1. Healing with complete soft tissue coverage over bone.
2. Resolution of sinus tract between bone and skin or mucosa.
3. Resolution of fracture or re-establishment of bony continuity.
4. Development of ORN in tooth socket following extraction or following implant.

Secondary outcome

1. Improvement in X-ray appearance.

Head and neck soft tissues

Primary outcomes

1. Wound dehiscence (breakdown of a surgical wound).
2. Surgical removal of larynx.
3. Major vessel bleeding.
4. Loss of dental implant into irradiated tissue (outcome added at second update as it is an emerging outcome of clinical relevance)

Secondary outcomes

1. Speed of wound healing.
2. Improvement in swelling or 'woodiness' of tissue.
3. Reversal of tracheostomy (surgical breathing hole in the trachea).

Urinary bladder

Primary outcomes

1. Resolution of bleeding.
2. Removal of bladder and urine diversion procedures.

Secondary outcomes

1. Improved cystoscopic appearance.
2. Frequency.
3. Dysuria (pain on passage of urine).

Chest wall

1. Nil additional to those listed under 'All anatomical areas'.

Bowel

Primary outcomes

1. Resolution of bleeding.
2. Operations on the bowel such as colostomy, ileostomy or bowel resection.

Secondary outcome

1. Improvement in pain score

Neurological tissue

Primary outcomes

1. Improvement in objective motor function.
2. Improvement in visual acuity.

Secondary outcomes

1. Improvement in sensory function.
2. Improvement in functional ability or activities of daily living (ADL).
3. Improvement in neuropsychiatric testing.
4. Improvement in X-ray or scan appearance.
5. Reduction in steroid dose.

Extremities

1. Nil additional to those listed under 'All anatomical areas'.

Adverse events of hyperbaric oxygen therapy

1. Recurrence of tumour (locally or remote).
2. Visual disturbance (short and long term).
3. Damage from pressure (aural, sinus or pulmonary barotrauma, in the short and long term).
4. Oxygen toxicity (short term).
5. Withdrawal from treatment for any reason.
6. Any other recorded adverse event.

Search methods for identification of studies

Electronic searches

We intended to capture both published and unpublished studies.

We initially searched in November 2004 and repeated the search in August 2008, March 2011 and December 2015.

We searched the following (from inception) in November 2004 and then repeated the searches in August 2008, March 2011 and December 2015:

1. the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 11);
2. MEDLINE (1966 to week 3, November 2015);
3. EMBASE (1980 to week 47, 2015);
4. EBSCO CINAHL (1982 to December 2015);
5. an additional database developed in our Hyperbaric facility, DORCTIHM (The Database of Randomised Trials in Hyperbaric Medicine (Bennett 2011) searched December 2015).

The search strategies for other databases were broad; Appendix 1, Appendix 2, Appendix 3, and Appendix 4, show the search strategies. The DORCTIHM search was by keywords as shown in Appendix 5.

Searching other resources

1. For the original review, we consulted experts in the field and leading hyperbaric therapy centres (as identified by personal communication and searching the Internet) and asked them for additional relevant data in terms of published or unpublished RCTs.
2. Handsearched relevant hyperbaric textbooks (Jain 2009; Kindwall 2008; Mathieu 2006; Neuman 2008), journals (*Undersea and Hyperbaric Medicine*, *Hyperbaric Medicine Review*, *Diving and Hyperbaric Medicine*, *Space and Environmental Medicine Journal*) and conference proceedings (Undersea and Hyperbaric Medical Society, SPUMS, European Undersea and Baromedical Society, International Congress of Hyperbaric Medicine) published since 1980.
3. Contacted authors of relevant studies to request details of unpublished or ongoing investigations.
4. Examined the reference list of all trials for inclusion in this review.

We applied no language restrictions. We contacted the study authors if there was any ambiguity about the published data.

Data collection and analysis

Selection of studies

One review author (MB) was responsible for handsearching and identification of appropriate studies for consideration and entered all possibly relevant studies into a bibliographic software package Reference Manager (Refman).Three review authors (MB, JF and NH) examined the electronic search results and identified comparative studies that may have been relevant. We retained studies when one or more review authors identified them as appropriate. We retrieved retained studies in full. Three review authors independently reviewed the studies. There review authors all had content expertise in HBOT, one had content expertise in radiation oncology (JF) and one (MB) had expertise in clinical epidemiology.

Data extraction and management

Each review author independently extracted the relevant data. We contacted primary authors to request information when missing data were encountered or if necessary data, such as adverse events, were not clearly stated. We resolved all differences by discussion and no disputed trials required referral to the Review Group contact editor for appraisal. Review authors recorded data using the data extraction form developed for this review.

Assessment of risk of bias in included studies

We appraised each included study to assess the risk of bias as outlined in Section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We presented our assessment of the risk of seven possible sources of bias in the risk of bias tables for each study, namely:

1. Random sequence generation (selection bias). How were the participants randomised to groups?
2. Allocation concealment (selection bias). Was the group allocation of participants unknown to the recruiting trialist?
3. Blinding (performance and detection bias). Was a reliable method of blinding therapy employed?
4. Blinding of participants and personnel (performance bias). Can we be confident participants and trial personnel were unaware of allocation?
5. Blinding of outcome assessors (detection bias). Were those measuring outcomes unaware of allocation?

6. Incomplete outcome data (attrition bias). Were missing data a potential source of bias?
7. Selective reporting (reporting bias). Were planned outcomes missing in the trial report?

Measures of treatment effect

We used CATmaker to calculate between-group comparisons for single trials when the report authors did not do so (CEBM 2004). For all other measures of treatment effect, we used Review Manager 5 (RevMan 2014). It was our intention where possible to analyse the data from different anatomical sites together (see outcomes listed under 'all anatomical areas'). However, many outcomes are specific to a particular anatomical site, and we analysed these outcomes separately. We used an intention-to-treat (ITT) analysis where possible and comparisons reflect efficacy in the context of randomised trialling, rather than true effectiveness in any particular clinical context. While we planned to compare survival over time using the log hazard ratio and variance (Parmar 1998), we found no suitable data. For dichotomous outcomes, we used risk ratios (RRs). For continuous data, we used the mean difference (MD) between treatment and control groups in each trial and aggregated MDs using inverse variance weights to estimate an overall MD and its 95% confidence interval (CI). We used a fixed-effect model where there was no evidence of significant clinical heterogeneity between studies (see below), and employed a random-effects model when such heterogeneity was likely. We used Review Manager 5 for all statistical analysis (RevMan 2014).

Where co-interventions differed significantly between studies, we clearly stated this and discussed the implications.

Overall primary outcomes (all anatomic areas)

1. Survival. For each trial, we calculated the RR for survival in the HBOT group compared to the control group. We pooled these RRs in a meta-analysis to estimate an overall RR and its 95% CI. As an estimate of the clinical relevance of any difference between experimental intervention and control intervention, we calculated the number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) with 95% CI as appropriate, using the formula NNTB = 1/risk difference (RD) with 95% CI calculated from the 95% CI of the RR, following the method recommended in Altman 2001.
2. Complete resolution of necrosis or tissue damage. We calculated the RR for complete resolution of necrosis or tissue damage with and without HBOT using the methods described in (1) above.
3. Improvement in LENT-SOMA scales. For each trial, we planned to calculate the MD between HBOT and control groups and combined them in a meta-analysis to estimate an overall MD and its 95% CI. No trials reported improvement in LENT-SOMA scales.

Overall secondary outcomes

1. Radiological improvement. Statistical analysis would depend on the nature of the data, but would have followed the methods outlined above ('Overall primary outcomes (all anatomic areas)'. No trials reported radiological improvement.

We planned to approach the outcomes for each anatomical site in an analogous manner to that outlined above.

1. Adverse events. For each trial, we planned to calculate the RR for each adverse event in the HBOT compared to the control group. We planned to pool these RRs in a meta-analysis to estimate an overall RR and its 95% CI. No trials reported adverse events.

Dealing with missing data

We employed sensitivity analyses using different approaches to imputing missing data. The best-case scenario assumed that none of the originally enrolled participants missing from the primary analysis in the treatment group had the negative outcome of interest while all participants missing from the control group did. The worst-case scenario was the reverse.

Assessment of heterogeneity

We assessed heterogeneity using the I^2 statistic and gave consideration to the appropriateness of pooling and meta-analysis.

Subgroup analysis and investigation of heterogeneity

We considered subgroup analysis based on:

1. anatomical location;
2. dose of oxygen received (pressure, time and length of treatment course);
3. nature of the comparative treatment modalities;
4. severity of injury.

Sensitivity analysis

We intended to perform sensitivity analyses for missing data and study quality based on the presence or absence of a reliable random allocation method, concealment of allocation and blinding of participants or outcome assessors where appropriate.

RESULTS

Description of studies

Following our updated search in August 2008, we had identified 116 publications apparently dealing with the use of HBOT for the treatment of LRTI. On the basis of screening the titles and abstracts, we excluded 98 records and retrieved the remaining 18 reports in full text. After appraisal of the full reports we further excluded five reports with non-random controls (Carl 2001; Gal 2003; Granstrom 1999; Maier 2000; Niimi 1997), two systematic reviews with no further randomised data (Coulthard 2002; Denton 2002), and one randomised trial with no quantitative data (Tobey 1979). See Characteristics of excluded studies table. The review included the remaining 10 records describing eight studies (Annane 2004; Clarke 2008; Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b; Pritchard 2001; Sidik 2007). Marx 1999a and Marx 1999b were trials reported for the first time in a textbook. The recruitment period for these studies was not known. As of August 2008, we had not been able to obtain a full-text copy of Sidik 2007, but we have moved this study from Characteristics of studies awaiting classification to Characteristics of included studies after the full report was obtained.

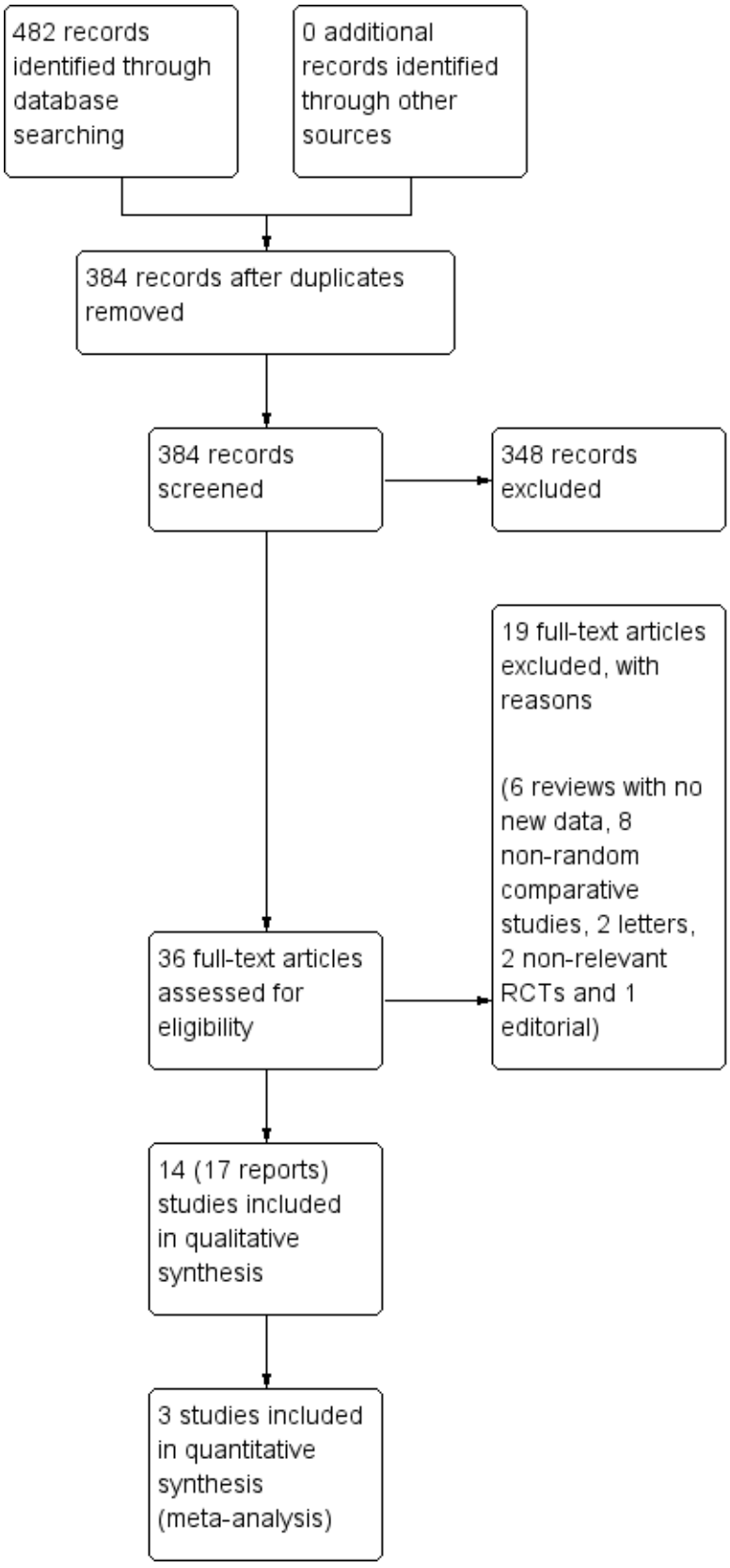
Our searches in March 2011 retrieved 180 records. After removal of duplicates, 145 records remained. On the basis of screening the titles and abstracts, we excluded 132 records and obtained the remaining 13 papers in full text. Of these reports, we included four (two studies, two secondary reports with new data) and added the

nine excluded reports to the Characteristics of excluded studies table.

Our most recent searches in December 2015 retrieved 186 records. After removal of duplicates, 128 additional records remained. On the basis of screening the titles and abstracts, we excluded 121 records and retrieved the remaining seven papers in full text. Of these reports, we included four (three studies, one secondary report with new data) and added three excluded reports Characteristics of excluded studies table.

Figure 1 shows the results of all four searches combined and summarised. In total, we included 17 reports of 14 trials (Annane 2004; Clarke 2008; Gothard 2010; Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b; Oton Sanchez 2013; Pritchard 2001; Schoen 2007; Shao 2011; Sidik 2007; Svalestad 2014; Teguh 2009). During the search, we also discovered six trials registered on ClinicalTrials.gov. We contacted the authors of each and included the remaining trials in the Characteristics of ongoing studies table.

Figure 1. Study flow diagram.



The included trials were published between 1985 and 2015 and, in total, the included trials had data on 753 participants, 390 (52%) receiving HBOT and 363 (48%) receiving control (see Characteristics of included studies table).

Four trials enrolled more females than males (Pritchard 2001 enrolled 34 participants and Gothard 2010 enrolled 58 participants, all female; Hulshof 2002 six females and one male; Clarke 2008 106 females and 13 males). Four trials enrolled more males than females (Annane 2004 59 males and 49 females; Schoen 2007 17 males and nine females; Teguh 2009 103 males, 32 females; Svalestad 2014 15 males and nine females). Oton Sanchez 2013; Sidik 2007 and Shao 2011 did not specify gender.

All trials required radiotherapy to have been given prior to enrolment, but the dose and any accompanying chemotherapy varied considerably between studies. Marx required a prior exposure to a minimum of 64 Gy in the area under investigation (Marx 1999a; Marx 1999b), Teguh 2009 accepted people with 46 to 70 Gy, and Shao 2011 and Svalestad 2014 required at least 50 Gy. None of the other studies specified a minimum dose.

Annane 2004 excluded people with more advanced disease. Clarke 2008 entered participants with radiation proctitis; Marx 1999a, Marx 1999b and Annane 2004 people with established ORN of the mandible; Hulshof 2002 people with cognitive deficits following brain irradiation with at least 30 Gy, and Pritchard 2001 enrolled people with radiation-induced brachial plexus lesions and Gothard 2010 enrolled people with arm lymphoedema, both following irradiation of the breast. Oton Sanchez 2013 enrolled people with cervical fibrosis in the neck, Shao 2011 people with haemorrhagic cystitis, Sidik 2007 people with stage I-IIIB carcinoma of the cervix and Svalestad 2014 people with a clinical diagnosis of LRTI of the head and neck tissues. The other three trials treated participants without radiation tissue necrosis: Marx 1985 enrolled participants requiring tooth extraction in an irradiated field, Teguh 2009 treated irradiated participants with head and neck lesions before they developed LRTI and Schoen 2007 treated participants having dental implants in an irradiated area (see 'Characteristics of included studies').

Both the dose of oxygen per treatment session and for the total course of treatment varied between studies. The lowest pressure administered was 2.0 ATA (Clarke 2008) and the highest was 3.0 ATA (Hulshof 2002), while all other trials utilised 2.4 or 2.5 ATA. The duration of all treatments was 80 to 90 minutes. All trials administered a total of 28 to 30 treatments, except Annane 2004 and Clarke 2008, where some people received 40 treatments and Oton Sanchez 2013 who administered 25 sessions. Annane 2004 used a twice-daily treatment schedule.

There were no active comparator regimens administered to the control groups but withheld from the HBOT group of these trials. Three trials administered a blinded sham therapy (Annane 2004; Clarke 2008; Pritchard 2001). Details are given in the Characteristics of included studies table.

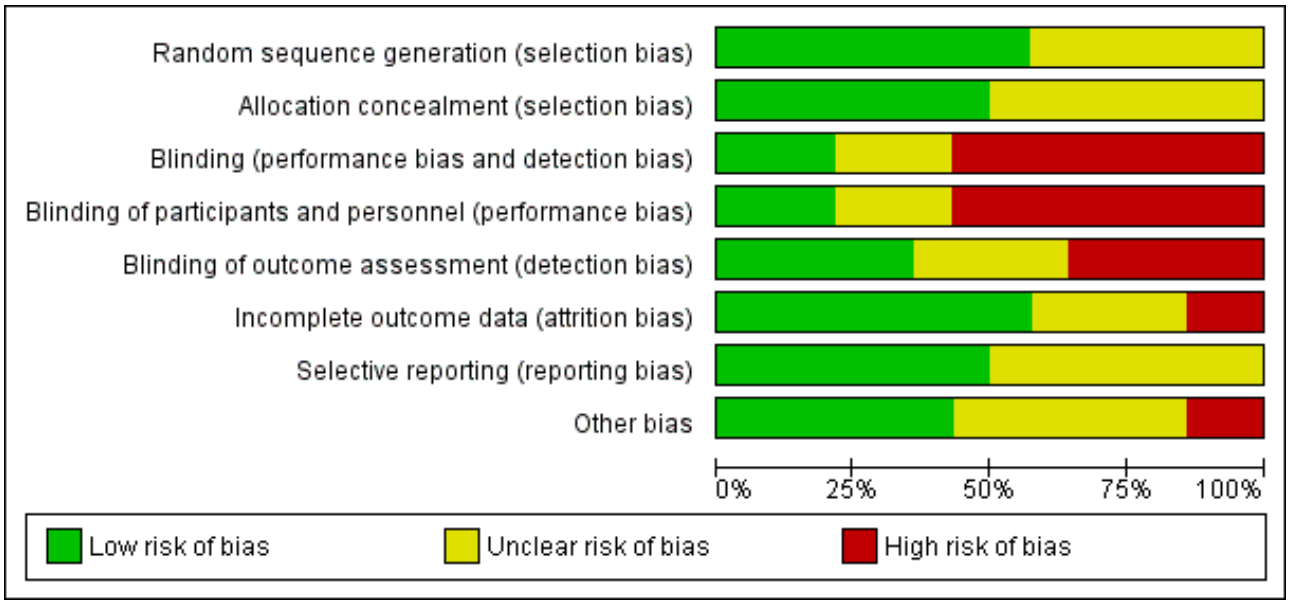
The follow-up periods varied from immediately after therapy (Clarke 2008; Sidik 2007), to three weeks following the treatment course (Marx 1999b), six months (Hulshof 2002; Marx 1985; Oton Sanchez 2013; Svalestad 2014), one year (Annane 2004; Gothard 2010; Pritchard 2001; Schoen 2007; Teguh 2009), and 18 months (Shao 2011). Marx 1999a did not specify the time at which outcome was measured. All included studies except Oton Sanchez 2013 and Svalestad 2014 reported at least one clinical outcome of interest. Of the outcomes identified above, these trials reported data on primary outcomes (resolution of problem, bony continuity established, mucosal cover, wound dehiscence and LENT-SOMA scale) and secondary outcomes (oedema resolution, pain scores, QoL, physical functioning, sensory function and neuropsychiatric testing).

Other outcomes (including non-clinical) reported included: radiological changes (Annane 2004), self rated memory and dexterity (Hulshof 2002), sensory action potentials (Pritchard 2001), postsurgical complication rate (Marx 1999a), wound infection rate (Marx 1999b), assessment of lymphoedema (lymphoscintigraphy and dielectric constant) (Gothard 2010), implant loss (Schoen 2007), and $PtcO_2$, laser Doppler flowmetry (LDF), microvascular density (MVD) and proliferation index (Svalestad 2014).

Risk of bias in included studies

The Characteristics of included studies table provides details of the quality assessment. Study quality varied widely; however, because very few analyses could be pooled, study quality was not used as a basis for sensitivity analysis. Figure 2 shows the risk of bias for each study presented graphically in, which suggests that blinding may be the greatest source of bias across these studies.

Figure 2. Summary of risk of bias in eight domains in the included studies



Allocation

Six studies adequately described allocation concealment (Annane 2004; Clarke 2008; Gothard 2010; Hulshof 2002; Pritchard 2001; Svalestad 2014), all except Svalestad 2014 used a remotely located randomisation officer. There was no clear indication for none of the remaining studies that the investigators were unable to predict the prospective group to which a participant would be allocated.

Six studies described randomisation procedures (Annane 2004; Clarke 2008; Gothard 2010; Pritchard 2001; Shao 2011; Svalestad 2014), all employing a computer-generated random number table. The remaining studies did not describe randomisation procedures.

Blinding

Three studies utilised a sham therapy in order to mask participants and outcome assessors to HBOT (Annane 2004; Clarke 2008; Pritchard 2001), while the remaining 11 studies employed no sham. Only Clarke 2008 formally tested the success of the blinding strategy.

Incomplete outcome data

Ten studies reported no losses to follow-up or violation of the study protocol (Annane 2004; Gothard 2010; Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b; Pritchard 2001; Shao 2011; Svalestad 2014; Teguh 2009). Clarke 2008 did not include 19 control participants and 11 HBOT group participants in the analysis because they did not complete the therapy protocol, and there was one further participant lost to follow-up at the end of treatment. Oton Sanchez 2013 lost 11 of 37 (30%) of subjects randomised because of 'failure to complete the study', and these were not reported. Sidik 2007 reported significant losses to follow-up at six months due to death from the primary diagnosis. Schoen 2007 reported that six participants were lost to final follow-up at one year. Sensitivity analysis using best- and worse-case scenarios were performed where this study contributed data to the analysis.

Only Pritchard 2001 specifically detailed an ITT analysis (two subjects in the HBOT group did not complete therapy, but were included in analysis). Ten of the remaining 14 studies reported full follow-up and did not report any protocol violation (see above).

Selective reporting

None of the 14 trials gave any information to suggest there were unreported outcomes. None had trial registration data with which to compare the outcomes reported.

Other potential sources of bias

Participant baseline characteristics

Given the variation in pathology outlined in Description of studies, it is not surprising there is considerable variation in participant baseline characteristics. Most trials were small and may be subject to bias arising from unbalanced allocation to groups for unknown confounders. See Characteristics of included studies table for details of participants enrolled.

Effects of interventions

See: **Summary of findings for the main comparison** Hyperbaric oxygen therapy versus standard approach for people with osteoradionecrosis

We first present the results for comparisons across combined anatomical areas and then proceed to individual anatomical areas that have been studied. Throughout this section, we have added data in the relevant analyses wherever available, even if there are only single studies, in anticipation of the possibility of pooling data in the future. However, in the text, we have reported the results as given by individual trial authors where pooling of data was not possible. Only six of the 14 trials reported were able to contribute to pooled data analyses, the remaining eight studies contributed to qualitative analysis only.

All anatomical areas

Primary outcomes

Death (Comparison 1, outcome 1)

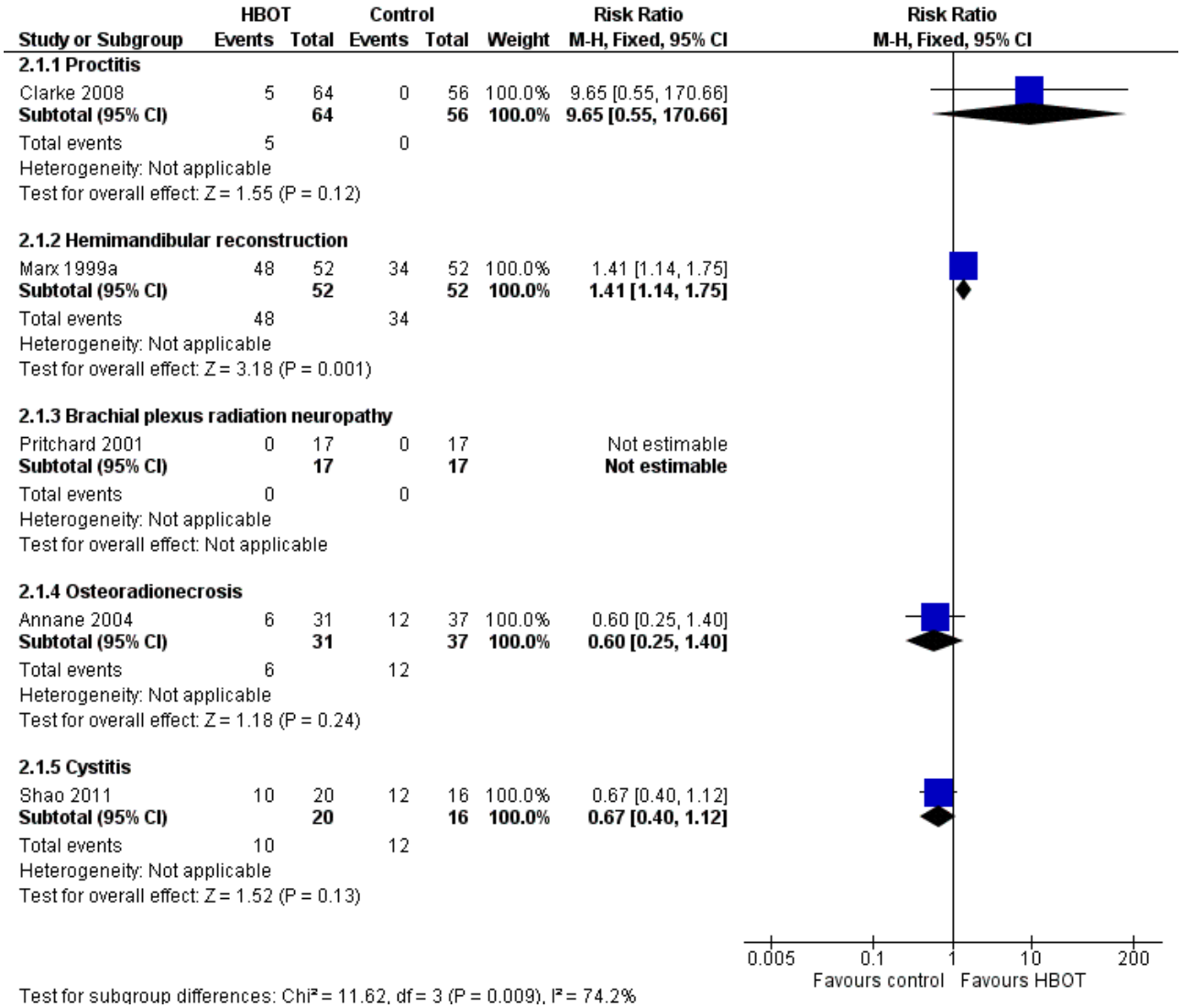
Annane 2004 reported two deaths in each group at one year, two from cancer re-growth and two from other causes not related to their ORN (P value = 0.99) Analysis 1.1). Clarke 2008 reported five deaths at one year, but this cross-over study did not identify the original treatment allocation, while Schoen 2007 reported that two enrolled participants died during the study, but their group allocation was not specified. No pooled analysis was possible.

Complete resolution of necrosis or tissue damage (Comparison 2, outcomes 2.1 and 2.2)

Complete resolution of clinical problem

Five trials reported complete resolution of clinical problem, involving 362 participants, with 184 (51%) randomised to HBOT and 178 (49%) to control (Annane 2004; Clarke 2008; Marx 1999a; Pritchard 2001; Shao 2011). Each of these individual trials enrolled participants with LRTI in different anatomical locations and we did not consider pooling of data to be appropriate. See Analysis 2.1 and Figure 3.

Figure 3. Forest plot of comparison: 2 Complete resolution of problem, outcome: 2.1 Complete resolution of clinical problem at end of therapy to three months.



Annane 2004 reported six of 31 (19%) participants with minor grades of ORN in the HBOT arm were resolved versus 12 of 37 (32%) in the control arm at one year (RR of healing with HBOT 0.60; 95% CI, 0.25 to 1.41; P value = 0.23).

Clarke 2008 reported the proportion of participants with radiation proctitis who were symptom free at the end of the course of HBOT as five of 64 (8%) versus none of 56 (0%) participants who had were not treated (P value = 0.0009).

Marx 1999a reported 48 of 52 (92%) participants requiring hemimandibulactomy for ORN were completely successful and healed compared to 34 of 54 (65%) controls who received the usual surgical treatment without HBOT (P value = 0.02).

Pritchard 2001 reported no cases of complete resolution of brachial plexopathy in either arm of a study enrolling 34 participants.

Shao 2011 reported nine of 20 (45%) participants with radiation cystitis were completely symptom free at 18 months after treatment versus eight of 16 (50%) participants who had a course of hyaluronic acid instillation into the bladder (P value = 0.63).

Development of osteoradionecrosis following dental implants

Schoen 2007 reported on development of ORN following dental implants in 26 previously irradiated participants deemed suitable for the placement of dental implants. One participant in the HBOT group developed ORN versus no participants in the control group (P value = 0.49) (Analysis 2.2).

Complete resolution or substantial improvement of necrosis or tissue damage (Comparison 3, outcome 3.1)

Two trials reported complete resolution or significant improvement of necrosis or tissue damage (Clarke 2008; Shao 2011). These two trials were clinically heterogeneous and we did not consider pooling of data was appropriate (Analysis 3.1).

Clarke 2008 reported this combined outcome immediately after completion of therapy. This trial enrolled 119 participants, with 64 randomised to HBOT and 56 to control. Twenty-nine (46%) participants in the HBOT group achieved complete resolution or significant improvement versus 15 (27%) in the control group, giving an absolute difference of 19% in favour of HBOT (P value = 0.04, NNTB 5).

Shao 2011 reported 15 of 20 (75%) participants with radiation cystitis were significantly better or symptom free at 18 months after treatment versus 12 of 16 (75%) participants who had a course of hyaluronic acid instillation into the bladder (P value > 0.99).

Improvement of LENT-SOMA scale (Comparison 4, outcome 4.1)

Improvement in LENT-SOMA score at completion of therapy

Only one trial reported improvement in LENT-SOMA score at completion of therapy, involving 150 participants, with 75 randomised to both HBOT and control (Clarke 2008). The mean improvement in LENT-SOMA score was greater in the HBOT group (5.0 with HBOT versus 2.6 with control, P value = 0.002) (Analysis 4.1).

Secondary outcomes

Resolution of pain (Comparison 5, outcomes 5.1, 5.2 and 5.3)

Change in pain score (0 to 100 scale) from baseline to six months after treatment

Two trials reported change in pain score from baseline to six months involving 70 participants with 37 randomised to HBOT and 33 to control (Pritchard 2001; Shao 2011). Pritchard 2001 used a sham hyperbaric exposure as control, while for Shao 2011, the comparator was the installation of hyaluronidase (HA) into the urinary bladder.

For Pritchard 2001, pain scores increased over this time period in both groups, but more so with HBOT (5.3 points with HBOT versus 1.2 points with control). The study did not report standard deviations (SD) around these means, precluding further analysis (Analysis 5.1).

For Shao 2011, pelvic pain improved in both groups (9 points (SD 7.9) with HBOT, P value < 0.01 versus 8.8 points (SD 1.4) with HA, P value < 0.05). A direct comparison between groups was not reported but comparison using CATmaker suggested this MD of 2.8 points in favour of HBOT was imprecise (95% CI -8.3 to 13.9).

Change in pain score (0 to 100 scale) from baseline to 12 months after treatment

Two trials reported change in pain score from baseline to 12 months involving 70 participants with 37 randomised to HBOT and 33 to control (Pritchard 2001; Shao 2011). Pritchard 2001 used a sham hyperbaric exposure as control, while for Shao 2011, the comparator was the installation of HA into the urinary bladder.

For Pritchard 2001, pain scores decreased over this time period in both groups, but more so with HBOT (5.0 points with HBOT versus 0.7 points with control). SDs were not reported around these means, precluding further analysis.

For Shao 2011, pelvic pain improved in both groups (9 points (SD 10.2) with HBOT, P value < 0.05 versus 13.1 points (SD 13.0) with HA, P value < 0.05). A direct comparison between groups was not reported by the authors but comparison using CATmaker suggested this MD of 1.6 points in favour of HA was imprecise (95% CI -9.8 to 13.0).

Change in pain score (0 to 100 scale) from baseline to 18 months after treatment

Only Shao 2011 reported change in pain score from baseline to 18 months, involving 36 participants (20 allocated to HBOT and 16 to installation of HA into the urinary bladder). Pelvic pain improved in both groups (11.5 points (SD 12.2) with HBOT, P value < 0.01 versus 15.0 points (SD 12.1) with HA, P value < 0.01). A direct comparison between groups was not reported but comparison using CATmaker suggested this MD of 1.0 points in favour of HA was imprecise (95% CI -10.1 to 12.1).

Resolution of swelling (Comparison 6, outcomes 6.1 and 6.2)

Resolution of lymphoedema in arm at six months

Only one trial reported resolution of lymphoedema in arm at six months, involving 34 participants with 17 randomised to both HBOT and control (Pritchard 2001). Two (12%) participants in the HBOT group achieved resolution, while none in the control group did so (P value = 0.29) (Analysis 6.1).

Relative reduction in arm volume at 12 months

Only one trial reported relative reduction in arm volume at 12 months, involving 46 participants (58 enrolled but 12 missing at 12 months), with 30 randomised to HBOT and 16 to control. There was no significantly greater reduction in the relative volume of the affected arm after treatment with HBOT (2.6% reduction in volume) compared with the control group (0.3% reduction) (MD in reduction 2.6%, P value = 0.86) (Analysis 6.2).

These authors also reported the proportion of participants achieving a greater than 8% reduction in volume of the arm (9/30 (30%) did so in the HBOT group versus 3/16 (19%) in the control group P value = 0.5) (Analysis 6.3).

Improvement in quality of life, function or both (Comparison 7, outcomes 7.1 to 7.6)

Short Form (SF)-36 score for general health at 12 months

Only one trial reported SF-36 score for general health at 12 months, involving 34 participants with 17 randomised to both HBOT and control (Pritchard 2001). The mean score for general health self rating was similar in both groups (58.8 with HBOT versus 61.1 with control). Using the standard errors given to calculate SD gave a P value = 0.79) (Analysis 7.1).

SF-36 score for physical functioning at 12 months

Only one trial reported SF-36 score for physical functioning at 12 months, involving 34 participants with 17 randomised to both HBOT and control (Pritchard 2001). The mean score for self rating of physical functioning was similar in both groups (53.5 with HBOT versus 57.5 with control). Using the standard errors given to calculate SD, this difference was not statistically significant (P value = 0.61) (Analysis 7.2). Gothard 2010 also reported no significant differences between the allocated groups at 12 months, but did not report the data.

Bowel bother subscale at completion of therapy

Only one trial reported bowel bother subscale at completion of therapy, involving 150 participants with 75 randomised to each of HBOT and sham therapy (Clarke 2008). This trial reported a mean improvement of 14.1% (P value = 0.0007) in this subscale following HBOT compared with a mean improvement of 5.8% (P value = 0.15) in the sham group (Analysis 7.3).

Lymphoedema-specific questionnaire at 12 months

Only one trial reported *lymphoedema at 12 months*, involving 58 participants, with 38 randomised to HBOT and 20 to control (Gothard 2010). This was a self assessment subscale of functional effect and was rated from 0 (no effect on life) to 100 (maximum effect on life). There was no significant difference between the groups at 12 months' estimation (HBOT median score 37.5; interquartile range (IQR) 20.8 to 52.1; control 45.8; IQR 13.0 to 62.5, P value not given) (Analysis 7.4).

Quality of life scores in head and neck cancers

Teguh 2009 enrolled 19 participants, eight (42%) randomised to HBOT and 11 (58%) to a no treatment control. The trial reported QoL in the form of items relating to xerostomia and dysphagia from EORTC, Head and Neck cancer module (H&N35) at several time points. They also determined a visual analogue scale (VAS) for 'dry mouth' and 'pain in the mouth'. We reported the results at 12 months here, but the P values are calculated from "regression analysis based on maximum likelihood estimation and incorporating the longitudinal character of the data." At 12 months, the H&N35 sticky saliva score (0 = nil, 100 = maximum) was 25 for participants who received HBOT versus 62 for controls (P value = 0.01), the H&N35 scores for dry mouth (same scale) were 28 for participants receiving HBOT versus 92 for controls (P value = 0.009), the H&N35 scores for difficulty swallowing (same scale) were 7 for participants receiving HBOT versus 40 for controls (P value = 0.011); the VAS for 'dry mouth' (0 = nil, 10 = maximum) were 3.4 for participants receiving HBOT versus 7.2 for controls (P value not given) and the VAS for 'pain in the mouth' (same scale) were 0.8 for participants receiving HBOT versus 6.6 for controls (P value < 0.0001) (Analysis 7.5).

Quality of life scores following dental implants into an irradiated area

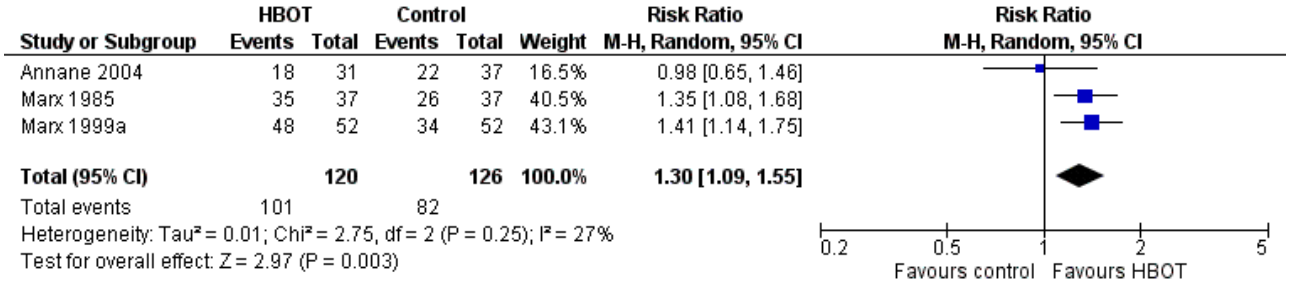
Schoen 2007 enrolled 26 participants, 13 randomised to HBOT plus antimicrobial therapy, and 13 to receive antimicrobial therapy alone. This trial reported on both global QoL estimates using the 30 question 'core questionnaire' of the EORTC H&N35 (0 to 100 scale, higher scores indicate better QoL) and the individual elements of that questionnaire. At 12 months, the global score was 66.7 (SD 13.6) in the HBOT group versus 84.3 (SD 19.7) in the control group (Analysis 7.6). The authors analysed the changes from baseline in each and found no significant differences between groups because entry scores were lower in the HBOT group.

Osteoradionecrosis (Comparison 8, outcomes 8.1 to 8.5)

Primary outcome: achievement of complete mucosal cover

Three trials reported achievement of complete mucosal cover, involving 246 participants, with 120 randomised to HBOT and 126 to control (Annane 2004; Marx 1985; Marx 1999a). A total of 101 (84%) participants in the HBOT group achieved mucosal cover versus 82 (65%) in the control group. Heterogeneity was moderate (I^2 = 27%), and explained by the addition of data from Annane 2004 (I^2 = 0% without Annane 2004). Overall, there was a significantly improved probability of attaining mucosal cover with the administration of HBOT (RR 1.3; 95% CI 1.1 to 1.6, P value = 0.003 (Analysis 8.1). The NNTB to achieve one further case with mucosal cover with the application of HBOT was 5 (95% CI 3 to 12) (Figure 4).

Figure 4. Forest plot of comparison: 8 Osteoradionecrosis, outcome: 8.1 Complete mucosal cover.



Primary outcome: establishment of bony continuity

Only one trial reported establishment of bony continuity, involving 104 participants, 52 randomised to both HBOT and control. Forty-eight (92%) participants in the HBOT group achieved continuity versus 34 (65%) in the control group (P value = 0.002 using Chi^2 method) (Analysis 8.2). The NNTB to achieve one further case with bony continuity with the application of HBOT was 4 (95% CI 2 to 8).

Primary outcome: resolution of sinus tract

No studies reported data for resolution of sinus tract.

Primary outcome: healing of tooth sockets following extraction in irradiated field at six months

Only one trial contributed results to healing of tooth sockets following extraction in irradiated field at six months, involving 74 participants, 37 randomised to both HBOT and control (Marx 1985). There was an increased chance of successful healing with HBOT with 35 (95%) participants in the HBOT group achieved healing of all sockets versus 26 (70%) in the control group (P value = 0.02 using Chi^2 method, Analysis 8.4). The NNTB with HBOT to achieve one further case with all tooth sockets healed was 4 (95% CI 2 to 13).

Secondary outcome: improvement in X-ray appearance

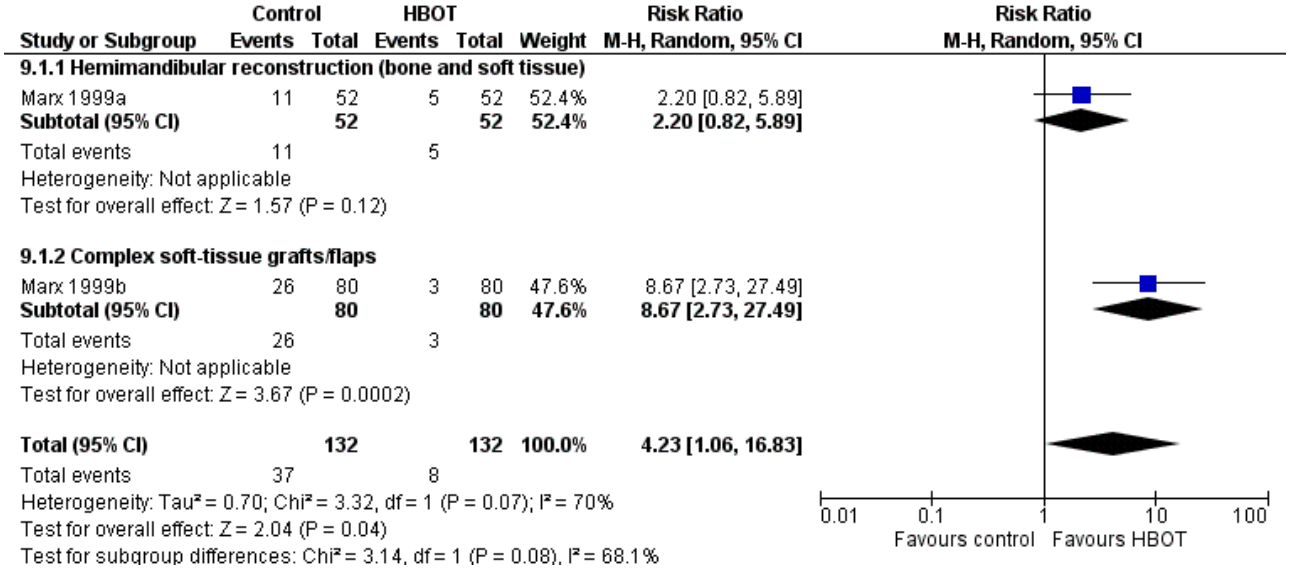
Schoen 2007 reported the radiological evidence of bone loss at 12 months from implant. The loss was 0.6 mm (SD 0.6) in the HBOT group versus 0.7 mm (SD 0.7) in the control group (P value = 0.73) (Analysis 8.5).

Head and neck soft tissues (Comparison 9, outcome 9.1 to 9.2)

Primary outcome: wound dehiscence

Two trials reported wound dehiscence, involving 368 participants, with 184 randomised to both HBOT and control groups (Marx 1999a; Marx 1999b). Overall, eight (6%) people in the HBOT group experienced wound breakdown versus 37 (28%) in the control group. Analysis for heterogeneity suggested a high proportion of variability between trials was not due to sampling variability (I^2 = 70%), and so this comparison was made using a random-effects model. There was a significantly improved chance of wound breakdown with control (RR 4.2; 95% CI 1.1 to 16.8, P value = 0.04) (Analysis 9.1). Stratification by tissue type involved confirmed the direction of effect was the same for both studies, but it remained significant only for soft tissue flaps and grafts (RR following hemimandibulectomy 2.2; 95% CI 0.8 to 5.9, P value = 0.12 (Marx 1999a); RR following soft tissue flap or graft 8.7; 95% CI 2.7 to 27.5, P value = 0.0002 (Marx 1999b)). The NNTB with HBOT to avoid one wound dehiscence overall was 5 (95% CI 1 to 59), and for soft tissue repairs alone was 4 (95% CI 3 to 6). See Figure 5.

Figure 5. Forest plot of comparison: 11 Head and Neck, outcome: 11.1 Wound dehiscence.



Primary outcome: surgical removal of larynx

No studies reported surgical removal of larynx.

Primary outcome: major vessel bleeding

No studies reported major vessel bleeding.

Primary outcome: loss of dental implant

Schoen 2007 reported on the number of people with lost implants following implant into an irradiated mandible in 26 participants. Eight implants were lost in the HBOT group (five participants) versus three implants (two participants) in the control group (P value = 0.38 comparing participant numbers) (Analysis 9.2).

No studies reported data for the following outcomes:

1. Surgical removal of the larynx
2. Major bleeding
3. Speed of wound healing
4. Improvements in tissue quality
5. Reversal of tracheostomy

Urinary bladder (comparison 10, outcomes 10.1 to 10.3)

Primary outcome: complete resolution of bleeding

One trial reported complete resolution of bleeding, including 36 participants with a clinical diagnosis of radiation cystitis following radiotherapy for an intra-pelvic malignancy (prostate, uterine cervix or bowel) (Shao 2011). Twenty (56%) participants were allocated to receive HBOT and 16 (44%) to installation of HA into the urinary bladder. The authors reported differences between groups for complete resolution of macroscopic haematuria at six months after treatment (15/20 (75%) participants in HBOT group versus 14/16 (88%) in HA group, P value > 0.05 Fisher's exact test), at 12 months (10/20 (50%) in HBOT group versus 12/16 (75%) in HA group, P value > 0.05), and at 18 months (9/20 (45%) in HBOT group versus 8/16 (50%) in HA group, P value > 0.05) (Analysis 10.1).

Primary outcome: removal of bladder and urine diversion procedures

No studies reported removal of bladder or urinary diversion.

Secondary outcome: daily voiding frequency change

One trial reported daily voiding frequency change, including 36 participants with a clinical diagnosis of radiation cystitis following radiotherapy for an intra-pelvic malignancy (prostate, uterine cervix or bowel) (Shao 2011). Twenty (56%) participants were allocated to receive HBOT and 16 (44%) to installation of HA into the urinary bladder. The authors reported the results of the Wilcoxon Signed Rank test of significance, although they appeared to have given the group estimates as mean and SD. Before treatment, the mean voids each day were 9.8 (SD 1.7) in HBOT group and 10.4 (SD 1.8) in HA group (Analysis 10.3). The authors reported a reduction in frequency in both arms of the study six months following treatment, but did not compare the two arms head-to-head (HBOT 8.6 (SD 1.5), P value < 0.01 and HA 7.5 (SD 0.9), P value < 0.01), but only the HA group at 12 months (HBOT 1.7 (SD 2.0), P value > 0.05 and HA 8.9 (SD 1.4), P value < 0.01) and for neither group at 18 months (HBOT 10.0 (SD 2.0), P value > 0.05 and HA 10.3 (SD 1.5), P value > 0.05) (Analysis 10.3).

No studies reported data for the following outcomes:

- Improved cystoscopic appearance
- Dysuria
- Chest wall changes
- Bowel bleeding, colostomy, ileostomy or bowel resection and pain

Neurological tissue (Comparison 13, outcome 13.1 to 13.4)

Primary outcome: improvement in objective motor function

No studies reported improvement in objective motor function.

Primary outcome: improvement in visual acuity

No studies reported improvement in visual acuity.

Secondary outcome: warm sensory threshold at one week after therapy

Only one trial reported warm sensory threshold at one week after therapy, involving 34 participants with 17 randomised to both HBOT and control (Pritchard 2001). The mean threshold temperature for reporting a warm sensation (lower figure indicates an improvement in function) at one week after therapy (compared to pre-treatment baseline) was reduced in the HBOT group, but not in the control group (-0.1°C with HBOT versus 1°C higher with control, MD 1.1°C; 95% CI -2.0 to 4.1, P value = 0.47) (Analysis 13.1).

Secondary outcome: warm sensory threshold at one year after therapy

Only one trial reported warm sensory threshold at one year after therapy, involving 34 participants with 17 randomised to both HBOT and control (Pritchard 2001). The mean threshold for reporting a warm sensation was increased in both groups, but less so in controls (0.5°C with HBOT versus 1.4°C with control, MD -0.9°C; 95% CI -4.0 to 2.2, P value = 0.58) (Analysis 13.2).

Secondary outcome: functional ability or activities of daily living

No studies reported functional ability or activities of daily living.

Secondary outcome: net number of neuropsychological tests (maximum 25 tests) improved at three months

Only one trial reported net number of neuropsychological tests (maximum 25 tests) improved at three months, involving seven participants with four randomised to HBOT and three to control (Hulshof 2002). The mean net number of improved tests was greater in the HBOT group (3.3 with HBOT versus 1.3 with control, MD 2.0; 95% CI 1.6 to 5.6, P value = 0.28) (Analysis 13.3).

Secondary outcome: net number of neuropsychological tests (maximum 25 tests) improved at six months

Only one trial reported net number of neuropsychological tests (maximum 25 tests) improved at six months, involving seven participants with four randomised to HBOT and three to control (Hulshof 2002). The mean net number of improved tests was greater in the HBOT group (3 with HBOT versus 2 with control, MD 1.0; 95% CI -3.6 to 5.6, P value = 0.67) (Analysis 13.4).

No studies reported on the outcome functional ability scores and ADL.

Adverse events

Only Annane 2004 reported comparative data on adverse event outcomes, three participants had some ear pain during treatment (two sham, one HBOT) and seven participants had a treatment session discontinued (five in the sham arm and two in HBOT. Reasons were 4 barotrauma, 1 seizure and two 'technical'). Clarke 2008 and Gothard 2010 gave overall figures for adverse events in all participants completing treatment. Nineteen (16%) participants reported of ear pain (Clarke 2008), while two (5%) were offered tympanostomy tubes in Gothard 2010. Four (3%) (Clarke 2008) and three (8%) (Gothard 2010) experienced transient myopia in these two studies, and two (1.7%) of confinement anxiety in Clarke 2008. Schoen 2007 and Teguh 2009 reported that the treatment was 'well tolerated' in their participants and Svalestad 2014 similarly reported no complications in either arm from the treatment given. Oton Sanchez 2013 reported "treatment was well tolerated and only two patients suspended by drug intolerance" - it was not clear if these two participants were also receiving HBOT. The other four trials made no comment on adverse effects.

Summary of studies not reporting our identified outcomes

The Svalestad 2014 trial was reported in two papers, one in 2014 and one in 2015.

This trial enrolled 22 participants with clinical LRTI who were referred for consideration of HBOT. Fourteen participants (64%) were allocated to HBOT and eight (36%) to delayed treatment for a minimum of six months. The first report included all participants and reported on LDF and $PtcO_2$ results before and after treatment. The later report added histopathological data on the 20 participants who consented to tissue biopsies in the irradiated gingival mucosa (see Svalestad 2014). It reported all outcomes as changes from baseline in each group rather than a direct comparison between groups.

This trial reported an increase in LDF (measured as blood flow expressed in 'perfusion units') in the HBOT group at six months after treatment, but not the controls (HBOT: baseline cheek blood flow 104 (SD 64) and at six months 306 (SD 237), P value < 0.05; control baseline 142 (SD 67) and six months 143 (SD 79), P value > 0.05). Similarly, there was an increase in $PtcO_2$ during the course of the study in the HBOT group, but not the control (HBOT baseline 14.0 mm Hg (SD 5.8) and six months 19.8 mm Hg (SD 6.5), P value < 0.05; control 14.0 mm Hg (SD 5.0) and 12.7 mm Hg (SD 4.6), P value > 0.05).

In the second report, both MVD and area were (similarly) significantly increased in the subepithelial tissue following HBOT, but not in the control group participants. For MVD, the HBOT group at baseline was 1.5 vessels/mm^2 (SD 0.6) and this increased at six months to 4.4 vessels/mm^2 (SD 1.9) (P value = 0.003) and the control group baseline was 1.5 vessels/mm^2 (SD 0.6) and at six months was 1.6 vessels/mm^2 (SD 0.5)(P value > 0.05). There were similar results for the total area of the microvasculature. The authors also reported the 'proliferation index', which is a measure of the rate at which cells proliferate in the tissue under study. The rate was unaffected by HBOT in this study.

DISCUSSION

Summary of main results

This review was updated in December 2015 and included three new studies. In total, we included data from 14 trials including 753 participants. However, the final conclusions have not been substantially altered.

In general, these trials suggest a benefit from HBOT for non-neurological radiation tissue injury. There was moderate quality evidence from three trials that complete mucosal cover of exposed bone was more likely to be achieved in people with ORN when HBOT was administered (RR 1.30, 95% CI 1.09 to 1.55) and from two trials that wound dehiscence was less likely following operations to repair mandibular ORN with the addition of HBOT (RR 4.23, 95% CI 1.06 to 16.83).

Other main results are taken from individual studies. Marx 1985 reported an increased chance of successful healing with HBOT compared to antibiotic cover for tooth extraction in an irradiated field (absolute risk reduction (ARR) 25%, P value = 0.02). Clarke 2008 reported some evidence that HBOT improved the probability of healing in radiation proctitis (ARR 8%) and a greater mean improvement in the severity of symptoms (LENT-SOMA score improvement: 5 points with HBOT and 2.6 points with control). Shao 2011 reported a reduction in pelvic pain following both HBOT and installation of HA into the urinary bladder for people with radiation cystitis, while Pritchard 2001 showed no improvements in pain associated with radiation brachial plexopathy with HBOT compared to control. Teguh 2009 reported improvements in xerostomia (P value = 0.009), dysphagia (P value = 0.011) and mouth pain (P value < 0.001) in people with radiation injury to the head and neck compared to untreated controls. Finally, Schoen 2007 reported no evidence that HBOT improved the chance of healing for dental implants into an irradiated field.

Several trials reported different measures of QoL and functional outcome following HBOT for radiation injury in the head and neck, bowel and axilla. Pooling was not appropriate for these outcomes. In general, these trials presented positive improvements with the head and neck and bowel, but not the neurological injury or lymphoedema associated with axillary radiation injury. One factor that may have influenced this was the well-established nature of the axillary injury in Pritchard 2001 and Gothard 2010 (88% had a time from radiotherapy to HBOT of 10 years or more in Pritchard 2001, mean time from radiotherapy to HBOT was more than 11 years in Gothard 2010).

Overall completeness and applicability of evidence

This review identified 14 trials investigating the use of HBOT for tissue damaged by LRTI, and we believe these represent all randomised trials in humans in this area, both published and unpublished, at the time of searching the listed databases.

These trials were published over a 25-year period up to 2014, and from a large geographical area. The trials studied a wide variety of people with LRTI and HBOT seems to have been generally well tolerated and safe. Clinical heterogeneity and differences in the outcomes measured meant that we performed few pooled analyses with these data and consequently our conclusions were limited.

We had planned to perform subgroup analyses with respect to anatomical location, dose of oxygen received (pressure, time and length of treatment course), nature of the comparative treatment modalities and the severity of injury. However, the paucity of eligible trials and poor reporting of some trials suggested that these analyses would not be informative. The oxygen dose used was reasonably standard over most trials. Participant inclusion criteria were not standard, and poorly reported in some trials. Specific comparator therapies were generally not employed.

The studies included in this review did not systematically report the incidence of adverse events. There are a number of minor complications that may occur commonly. Visual disturbance, usually reduction in visual acuity secondary to conformational changes in the lens, is very commonly reported - perhaps as many as 50% of people having a course of 30 treatments (Khan 2003). While the great majority of people recover spontaneously over a period of days to weeks, a small proportion of people continue to require correction to restore sight to pre-treatment levels. The second most common adverse event associated with HBOT is middle-ear barotrauma. Barotrauma can affect any air-filled cavity in the body (including the middle ear, lungs and respiratory sinuses) and occurs as a direct result of compression. Ear barotrauma is by far the most common as the middle ear air space is small, largely surrounded by bone and the sensitive tympanic membrane, and usually requires active effort by the person in order to inflate the middle ear through the Eustachian tube on each side. Barotrauma is thus not a consequence of HBOT directly, but rather of the physical conditions required to administer it. Most episodes of barotrauma

are mild, easily treated or recover spontaneously and do not require the therapy to be abandoned.

Quality of the evidence

Many of the trials enrolled modest numbers of participants, particularly the trial investigating cerebral radiation injury, which reported only seven participants (Hulshof 2002). Our confidence in the two pooled estimates was downgraded due to poor reporting of potential biases in two trials and imprecision in the estimated improvements with HBOT (Summary of findings for the main comparison). Other problems for this review were the poor methodological quality of some of these trials (particularly Marx 1999a; Marx 1999b), variability in entry criteria, and the nature and timing of outcomes, and poor reporting of both outcomes and methodology. In particular, there is a possibility of bias due to different anatomical locations and extent of tissue damage on entry to these trials, as well as from non-blinded management decisions in three of the trials (Marx 1985; Marx 1999a; Marx 1999b). Further, it is not clear when the participants for Marx 1999a and Marx 1999b were recruited - these trials may represent work from some years earlier.

Potential biases in the review process

While we have made every effort to locate further unpublished data, it remains possible this review is subject to a positive publication bias, with generally favourable trials more likely to achieve reporting. With regard to long-term outcomes following HBOT and any effect on the QoL for these people, we have located few relevant data. Encouragingly, we have identified six ongoing trials that seem likely eligible for inclusion in future updates of this review (Forner 2011; Gesell 2004; HOPON 2011; Kuhnt 2008; Oscarsson 2012; Yarnold 2010).

Agreements and disagreements with other studies or reviews

Our review is broadly consistent with recent systematic reviews in this area. Hoggan 2014 found 11 articles comparing HBOT with no HBOT for the treatment of LRTI and concluded that "HBOT is a safe intervention which may offer clinical benefits to patients suffering from radiation proctitis and non-neurological STRI [soft tissue radiation-related injuries] of the head and neck". They called for further high-quality trials to determine more precisely the role of HBOT in this area. In a review of HBOT for gynaecological malignancies, Craighead 2011 suggested that HBOT is "likely effective for late radiation tissue injury of the pelvis" in otherwise refractory injury and may reduce postoperative complications in people with LRTI requiring operative surgery.

Any benefit from HBOT for the treatment of ORN is not reflected in the results of Annane 2004. There are several reasons why this might be so. First, this trial did not test the usual treatment regimen employed for the management of ORN and may not therefore be directly comparable with the other trials in this review. Case series data from the 1980s suggest that HBOT in isolation is not associated with a high resolution rate for established ORN and most centres now employ a combination of operative therapy, antibiotics and HBOT, as described by Marx (the Wilford Hall Protocol) (Marx 1983). One automatic definition of poor outcome for Annane 2004 was the requirement for operative therapy in cases presenting with less-extensive disease, whether or not full recovery was eventually achieved. However, these cases would be reported as successes in the other included trials. Second, 66 of the 134 (49%) participants presenting with ORN during the study period were ineligible for inclusion, making generalisation of the findings of this trial to more advanced cases of ORN (such as those presented in Marx 1999a and Marx 1999b) problematic. The first author has subsequently confirmed that "...one cannot use the findings of our study to decide the optimal treatment of severe forms of mandibular necrosis" (personal communication, April 2008). Third, of the 50 participants in this trial that did not have a good outcome at one year, 34 were described as experiencing previous treatment failure, which may have biased the result against superiority for either group. Finally, this trial was stopped (according to pre-defined rules) with only 68 participants included and before a statistically significant result had been achieved. Any of these factors may have influenced the outcome of this trial. It is also possible that advances in care have taken place over time, such that HBOT no longer carries a therapeutic benefit.

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence of moderate quality that hyperbaric oxygen therapy (HBOT) improves outcome in late radiation tissue injury (LRTI) affecting bone and soft tissues of the head and neck, for radiation proctitis and to prevent the development of osteoradionecrosis following tooth extraction in an irradiated field. There was no such evidence of any important clinical effect on neurological tissues, either peripheral or central. Thus, the application of HBOT to selected people and tissues may be justified. While the small number of studies, the modest numbers of participants, and the methodological and reporting inadequacies of some of the primary studies included in this review demand a cautious interpretation, the pathology of radiation injury suggests that other tissues are also likely to respond. Further research is required to establish the optimum participant selection and timing of any such therapy. An economic evaluation should also be undertaken.

Implications for research

There is a strong case for further large randomised trials of high methodological rigour in order to define the true extent of benefit from the administration of HBOT for people with LRTI. Specifically, more information is required on the subset of disease severity and tissue type affected that is most likely to benefit from this therapy, the time for which we can expect any benefits to persist and the oxygen dose most appropriate. Any future trials would need to consider in particular:

1. appropriate sample sizes with power to detect expected differences generated by this review;
2. careful definition and selection of target participants;
3. appropriate oxygen dose per treatment session (pressure and time);
4. appropriate supportive therapy to which HBOT would be an adjunct;
5. use of an effective sham therapy;
6. effective and explicit blinding of outcome assessors;
7. appropriate outcome measures including all those listed in this review;
8. careful elucidation of any adverse events;

9. the cost-utility of the therapy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Annane 2004

Methods	Multicentre RCT with central computerised allocation concealment and participant/outcome assessor blinding
Participants	People with overt ORN for at least 2 months despite antibiotics, local irrigation and surgery
Interventions	Control: 9% oxygen breathing at 2.4 ATA for 90 minutes 30 times over 3 weeks. If an operation was required, a further 10 treatments were given postoperatively HBOT: 100% oxygen on the same schedule
Outcomes	Resolution of the problem, establishment of mucosal cover
Notes	This trial did not test the standard therapeutic approach because most participants were deemed to have failed if they required operative therapy

Risk of bias

Bias	Authors' judgement	Support for judgement

Annane 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	Clear description. "The random allocation sequence (1:1) was generated by the statistician ...using a computer-generated list equilibrated every four patients"
Allocation concealment (selection bias)	Low risk	"Patients were assigned to their treatment group by the pharmacist, and the allocation sequence remained concealed for all investigators, patients, nursing staff, and the members of the SEMB [safety and efficacy monitoring board] throughout the study period"
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double blind, and there was a convincing description of the sham procedure: "HBO [hyperbaric oxygen] was performed using a multiplace chamber (CXPRO; COMEX, Marseilles, France) pressurized with compressed air, and, at plateau, the patients received, via a tight-fitting oronasal mask, either 100% oxygen without oxygen pauses (active treatment) or a gas containing 9% oxygen and 91% nitrogen (the placebo), which yielded similar arterial oxygenation than breathing room air at 1 ATA"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double blind, and there was a convincing description of the sham procedure: "HBO [hyperbaric oxygen] was performed using a multiplace chamber (CXPRO; COMEX, Marseilles, France) pressurized with compressed air, and, at plateau, the patients received, via a tight-fitting oronasal mask, either 100% oxygen without oxygen pauses (active treatment) or a gas containing 9% oxygen and 91% nitrogen (the placebo), which yielded similar arterial oxygenation than breathing room air at 1 ATA"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All study outcomes were blindly assessed by the same surgeon (P.A.)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in final outcome. "Among the 68 randomly assigned patients, at 1 year there were six (19.3%) of 31 patients who had recovered in the HBO [hyperbaric oxygen] arm and 12 (32.4%) of 37 in the placebo arm."
Selective reporting (reporting bias)	Low risk	All outcomes indicated were reported in this paper
Other bias	High risk	The nature of the primary outcome was very unusual. The issue is discussed in the text

Clarke 2008

Methods	Multicentre RCT with central computerised allocation concealment and participant/outcome assessor blinding
Participants	150 people with a 3-month history of radiation proctitis unresponsive to therapy
Interventions	Control: air breathing at 1.1 ATA for 90 minutes 30 times over 6 weeks. Sham compression to trivial pressure and return HBOT: 100% oxygen at 2.0 ATA for 30 or 40 sessions over 6-8 weeks
Outcomes	Healing or significant improvement LENT-SOMA Scores

Clarke 2008 *(Continued)*

	QoL assessment
Notes	Full report of the proctitis group of this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Biostatisticians at the University of South Carolina generated the randomization sequence, which was uploaded into, and concealed within, the study database software. The patients were randomly assigned (1:1) to receive HBO [hyperbaric oxygen] or normobaric air, using a "blocking" process. The block size was four and was equally stratified with two of each treatment options (A or B)"
Allocation concealment (selection bias)	Low risk	Apparent from the following description. "The randomization sequence became available to the unblinded local principal investigator only on irretrievable entry of each patient's demographic information, medical history, and clinical characteristics"
Blinding (performance bias and detection bias) All outcomes	Low risk	There was a good description of the sham treatment. "For patient blinding purposes, Group 2 patients underwent a brief compression to 1.34 ATA at the beginning of each treatment. The chamber was then slowly decompressed from 1.34 to 1.1 ATA." "Reassessment, after 30 treatment sessions, was undertaken by the referring physician, who remained unaware of the allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	There was a good description of the sham treatment. "For patient blinding purposes, Group 2 patients underwent a brief compression to 1.34 ATA at the beginning of each treatment. The chamber was then slowly decompressed from 1.34 to 1.1 ATA"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Reassessment, after 30 treatment sessions, was undertaken by the referring physician, who remained unaware of the allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full follow-up at the end of treatment. Reasonable rate of attrition and equal across groups. "Of the 150 patients, 120 completed the protocol (Fig. 2). At 1 year, 5 patients (4%) had died and 9 (8%) had been lost to follow-up"
Selective reporting (reporting bias)	Low risk	No missing outcomes
Other bias	Unclear risk	Randomised data were not available for outcomes beyond the end of therapy because the study was then unblinded and cross-over offered to those not in the active treatment group

Gothard 2010

Methods	Multicentre RCT - 2:1 ratio of allocation to study vs. control group
Participants	58 people with unilateral arm lymphoedema of a > 15% increase in arm volume and persisting for at least 3 months with good treatment for lymphoedema
Interventions	All participants in both groups received 'good standard care' for lymphoedema and in the active group the participants also received HBOT at 2.4 ATA with 90 minutes of 100% oxygen breathing for a total of 30 treatment sessions over 6 weeks

Gothard 2010 *(Continued)*

Outcomes	Change in arm volume and QoL assessment at 1 year
Notes	Trial prompted by non-random observation and the results of Pritchard 2001

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation run from central allocation body: "Research volunteers were randomised with a ratio of 2:1 (treatment:control) ...by a telephone call to the randomisation service of The Institute of Cancer Research Clinical Trials & Statistics Unit"
Allocation concealment (selection bias)	Low risk	Randomisation made after consent: "Research volunteers were randomised with a ratio of 2:1 (treatment:control) after confirmation of eligibility and consent procedure..."
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding and 1 of the main outcomes was QoL. Bias less likely for arm volume and other objective outcomes: "Volunteers in the treatment group were compressed to 2.4 atmospheres absolute (ATA) (243 kPa) in a hyperbaric chamber ..... Volunteers in the control group continued best standard care for lymphoedema"
Blinding of participants and personnel (performance bias) All outcomes	High risk	See above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk of arm volume, quantitative lymphoscintigraphy and dielectric constant meter measurements to determine ongoing lymphoedema
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full account and most participants were followed up at 1 year: "Of the 58 patients randomised, baseline assessments were done in 53 (91.4%): 17 control and 36 HBO. Of the 53 patients with baseline assessments, 46 had 12-month assessments (86.8%): 16 control and 30 HBO. Reasons why patients did not have assessments at baseline and 12 months are shown in Fig. 1"
Selective reporting (reporting bias)	Low risk	No evidence for this
Other bias	Low risk	No indication of other bias

Hulshof 2002

Methods	RCT using random number table with allocation concealment but no blinding. Randomised in matched pairs
Participants	7 people with cognitive deficits present at least 1.5 years after irradiation of the brain with at least 3000 cGy
Interventions	Control: nil specific HBOT: 100% oxygen at 3 ATA for 115 minutes for 30 sessions over 6 weeks (5 days out of 7 each week)

Hulshof 2002 *(Continued)*

Outcomes	Neuropsychiatric testing
Notes	Very low power study with many outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The actual method used was unclear. "Patients were randomly assigned to an experimental group who were treated immediate (immediate group) and a control group with delayed treatment (delayed group). The randomization was blinded and performed by an independent employee at the neurology department"
Allocation concealment (selection bias)	Unclear risk	Implied but not clearly described. "Patients were randomly assigned to an experimental group who were treated immediate (immediate group) and a control group with delayed treatment (delayed group). The randomization was blinded and performed by an independent employee at the neurology department"
Blinding (performance bias and detection bias) All outcomes	High risk	No attempt at blinding
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt at blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No attempt at blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses at reporting. "All seven eligible patients completed the full period of 30 HBO [hyperbaric oxygen] sessions as well as the three neuropsychological tests"
Selective reporting (reporting bias)	Low risk	No missing outcomes
Other bias	Unclear risk	Very small trial with very low power. "The immediate group consisted of four patients and the delayed group of three patients"

Marx 1985

Methods	Multicentre randomised trial. No details of methodology for randomisation, allocation concealment or blinding
Participants	74 people requiring tooth extraction in a field irradiated with at least 6000 cGy > 6 months and < 15 years previously. Also excluded with penicillin or HBOT contraindications, active tumour present, recent chemotherapy or concurrent disease (e.g. diabetes) that might affect wound healing
Interventions	Control: teeth extracted in standard way with penicillin 1 million units pre-extraction and 500 mg 4 times each day for 10 days postextraction

Marx 1985 *(Continued)*

	HBOT: 20 preoperative treatment sessions at 2.4 ATA for 90 minutes daily 5 or 6 days each week, followed by 10 further sessions postoperatively
Outcomes	Development of clinical ORN with non-healing at 6 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information apart from use of the word "randomized"
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Unclear risk	No information given

Marx 1999a

Methods	Described as randomised. No details concerning blinding or allocation concealment
Participants	104 people requiring hemimandibular jaw reconstruction in tissue beds exposed to at least 6400 cGy radiotherapy. No other specific exclusions
Interventions	Control: not state HBOT: 20 preoperative treatment sessions at 2.4 ATA for 90 minutes daily 5 days each week, followed by 10 further sessions postoperatively
Outcomes	"Success" defined as achievement of continuity, restoration of alveolar bone height, restoration of osseous bulk, restoration of arch form, maintenance of bone form for 18 months and restoration of facial contours Complication rate (infection or dehiscence)
Notes	Sketchy account within a textbook chapter written by the author

Marx 1999a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information apart from use of the word "randomized"
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Unclear risk	No information given

Marx 1999b

Methods	Described as randomised. No details concerning blinding or allocation concealment
Participants	160 people requiring major soft tissue surgery or flaps into an irradiated area (> 6400 cGy). No other specific exclusions
Interventions	Control: not stated HBOT: 20 preoperative treatment sessions at 2.4 ATA for 90 minutes daily 5 days each week, followed by 10 further sessions postoperatively
Outcomes	Wound infection, dehiscence, delayed healing
Notes	Sketchy account within a textbook chapter written by the author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information apart from use of the word "randomized"

Marx 1999b *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Unclear risk	No information given

Oton Sanchez 2013

Methods	Unblinded, randomised controlled study
Participants	37 people with cervical fibrosis following irradiation for tumours in the head and neck. 26 completed trial (13 in each arm)
Interventions	Both arms received both pentoxifylline 400 mg and tocopherol 400 mg twice daily for 6 months. 1 group also received HBOT - 100% oxygen at 2.4 ATA for 90 minutes, 5 times a week from week 3 to week 9 of the drug treatment (total 25 treatments)
Outcomes	Improvement in fibrosis at 3 and 6 months
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method unclear - "An open, controlled, randomized clinical trial"
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding (performance bias and detection bias) All outcomes	High risk	No sham attempted

Oton Sanchez 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	"An open, controlled, randomized clinical trial"
Incomplete outcome data (attrition bias) All outcomes	High risk	"37 patients were randomised and 26 completed the trial". None of the missing patients were included in analysis.
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	High risk	This trial report is an abstract only and may not have been subject to peer review.

Pritchard 2001

Methods	Randomised, allocation concealed with blinding of outcome assessors and participants
Participants	34 people with established radiation-related brachial plexopathy, median duration 3 years. People with active tumour or contraindications to HBOT excluded
Interventions	Control: 100 minutes at 2.4 ATA breathing 41% oxygen to simulate 100% oxygen at 1 ATA, daily 5 days per week to a total of 30 sessions HBOT: 100% oxygen breathing on the same schedule
Outcomes	Sensory thresholds, QoL scores, McGill Pain Score, lymphoedema resolution
Notes	Many other outcomes reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Research volunteers were randomized on the first day of treatment by a telephone call to the Clinical Trials & Statistics Unit, Institute of Cancer Research, using a 1:1 randomization to HBO_2 or control group"
Allocation concealment (selection bias)	Low risk	"Research volunteers were randomized on the first day of treatment by a telephone call to the Clinical Trials & Statistics Unit, Institute of Cancer Research, using a 1:1 randomization to HBO_2 or control group."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Individuals allocated to the control group accompanied the HBO_2 group patients and experienced the same number and type of pressure exposures"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Individuals allocated to the control group accompanied the HBO_2 group patients and experienced the same number and type of pressure exposures."

Pritchard 2001 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All investigators (except the operators of the hyperbaric chamber and the trial statistician) remained blind to treatment assignments until the final analysis."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Only 1/72 assessments over 12 months of planned follow up was missed."
Selective reporting (reporting bias)	Low risk	No evidecne of selective reporting
Other bias	Low risk	No other significnat bias detected.

Schoen 2007

Methods	Unblinded RCT
Participants	26 people with a history of irradiation for a primary tumour of the head and neck who were suitable for dental implants in the lower jaw
Interventions	All received perioperative antibiotics and the HBOT group received 20 sessions on 100% oxygen at 2.5 ATA for 80 minutes daily before operation and for 10 days after operation
Outcomes	Postoperative complications, implant survival at 1 year, periodontal health indicators, functional assessment and QoL
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer program was used for randomization of the patients"
Allocation concealment (selection bias)	Low risk	Not specifically stated, but the implication is clear that allocation only took place after consent: "Patients who agreed with treatment were randomized in two groups"
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding and some outcomes are subjective (e.g. QoL): "These patients either received peri-operative antibiotics or antibiotics in combination with HBO treatment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no attempt to blind participants or those delivering care. Some outcomes are subjective (e.g. QoL): "These patients either received peri-operative antibiotics or antibiotics in combination with HBO treatment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor may have been unaware of allocation: "All clinical assessments were performed by the investigator (PJS) who was not involved in treatment of the patients"
Incomplete outcome data (attrition bias) All outcomes	High risk	Significant losses to follow-up. "Two patients past (sic) away during the osseointegration because of medical complications not related to the implant surgery. In 23 patients implant-retained overdentures were fabricated, while in one patient no prosthesis could be made because of loss of all implants relat-

Schoen 2007 *(Continued)*

		ed to development of osteoradionecrosis. At the 1 year evaluation, six patients were lost to follow-up due to serious illness not related to implant surgery"
Selective reporting (reporting bias)	Unclear risk	No indication that outcome measures have not been reported
Other bias	Low risk	No indication of other bias

Shao 2011

Methods	Unblinded RCT
Participants	36 people with haemorrhagic radiation cystitis developing after irradiation for pelvic cancers
Interventions	HBOT: 100% oxygen administered at 2.5 ATA for 60 minutes daily to a total of 30 treatments Comparator: instillation of HA 40 mg into the bladder weekly for 4 weeks then monthly for 2 months
Outcomes	Complete response to treatment defined as resolution of all symptoms up to 18 months Partial response defined as resolution of clots but not macroscopic haematuria Individual measures reported for pain (VAS 1-10 scale); haematuria (graded 1 (microscopic) to IV (life-threatening bleeding); frequency of voiding
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"We used computer-generated random numbers to perform the randomisation."
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealement.
Blinding (performance bias and detection bias) All outcomes	High risk	No attempt at sham treatment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt at any blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No evidence of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants reached final follow-up
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting

Shao 2011 *(Continued)*

Other bias	Low risk	No other major source of bias identified

Sidik 2007

Methods	Unblinded RCT designed to evaluate the effect of HBOT on QoL after pelvic irradiation
Participants	People with stage I-IIIB carcinoma of the cervix who had undergone irradiation
Interventions	There was no sham intervention. Those randomised to HBOT received 20 treatments but the exact protocol is not given
Outcomes	Symptom severity scale (LENT-SOMA) and Karnofsky QoL assessment
Notes	Poorly reported trial with no control therapy or blinding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Little information: "The block randomisation was performed"
Allocation concealment (selection bias)	Unclear risk	No information on this
Blinding (performance bias and detection bias) All outcomes	High risk	No attempt at blinding
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt at blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No attempt at blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Significant loss to follow-up at 6 months with several participants dying of their primary problem
Selective reporting (reporting bias)	Unclear risk	Insufficient information is given to be certain
Other bias	Unclear risk	Poor reporting makes an assessment difficult

Svalestad 2014

Methods	Unblinded RCT
Participants	22 people with soft tissue radiation injury or ORN affecting the oral mucosa. Minimum 50 Gy exposure and a clinical indication for HBOT

Svalestad 2014 *(Continued)*

Interventions	100% oxygen at 2.5 ATA for 90 minutes daily for 20-40 (mean 29) sessions over 6 weeks Control
Outcomes	Laser Doppler flowmetry, transcutaneous oximetry, microvascular density and vessel area
Notes	2 participants refused tissue biopsies so do not contribute data to tissue microvascular measures

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Group assignment was made after enrolment using a predetermined randomized allocation sequence".
Allocation concealment (selection bias)	Low risk	"Group assignment was made after enrolment using a predetermined randomized allocation sequence"..
Blinding (performance bias and detection bias) All outcomes	High risk	No sham treatment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt at blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No suggestion this was attempted
Incomplete outcome data (attrition bias) All outcomes	Low risk	No suggestion there were any missing data
Selective reporting (reporting bias)	Unclear risk	No trial registration indicated
Other bias	Low risk	No other source of bias detected

Teguh 2009

Methods	Unblinded RCT
Participants	19 people with a diagnosis of nasopharyngeal or oropharyngeal carcinoma and treated with radiotherapy (47-70 Gy) with or without chemotherapy. HBOT given 2 days after completion of radiotherapy/chemotherapy
Interventions	100% oxygen at 2.5 ATA for 90 minutes daily for 30 sessions over 6 weeks Control
Outcomes	QoL estimates, dryness of mouth
Notes	Trial stopped early because of slow recruitment

Teguh 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Seems reliable from the description. "Patients were randomized by the trial office..... by use of a block of several randomized sizes. Patients were stratified by tumor site (i.e., oropharynx or nasopharynx) and treatment modality (i.e., IMRT [intensity-modulated radiation therapy] or Cyberknife/Brachytherapy or postoperative radiotherapy)"
Allocation concealment (selection bias)	Low risk	"This randomization took place directly after inclusion of the patients in the study"
Blinding (performance bias and detection bias) All outcomes	High risk	Subjective outcome and no attempt at blinding
Blinding of participants and personnel (performance bias) All outcomes	High risk	All participants and treating staff aware of allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention that outcome assessor was blinding and this seems unlikely
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	No evidence for missing outcomes
Other bias	Low risk	No evidence of other biases, but relatively poor methodological reporting

ATA: atmospheres absolute; brachial plexopathy: poor functioning of the nerves going through the armpit to supply the arm and resulting in loss of sensation, muscle power and function in the arm; cGy: Centi-Gray; HA: hyaluronidase;
HBOT: hyperbaric oxygen therapy;
LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic;
ORN: osteoradionecrosis;
QoL: quality of life;
RCT: randomised controlled trial.

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

Study	Reason for exclusion
Carl 2001	Case series only, no randomised comparator
Coulthard 2002	Systematic review - no new data
Craighead 2011	Not an RCT
Denton 2002	Systematic review - no new data
Gal 2003	Retrospective cohort study

Study	Reason for exclusion
Granstrom 1999	Case control study - not randomly allocated
Maier 2000	Retrospective cohort study
Marson 2014	Not an RCT
Niimi 1997	Cohort study
Rajaganapathy 2014	Not about HBOT
Tobey 1979	RCT but no quantitative data given. Both groups received some HBOT (1.2 ATA versus 2.0 ATA)

ATA: atmospheres absolute;
HBOT: hyperbaric oxygen therapy;
RCT: randomised controlled trial.

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

Forner 2011

Trial name or title	Hyperbaric Oxygen Treatment of Mandibular Osteoradionecrosis. NCT00760682
Methods	RCT
Participants	Established mandibular ORN
Interventions	HBOT
Outcomes	Complete resolution or radiographic evidence only
Starting date	June 2008
Contact information	Forner L; lone.forner@rh.regionh.dk
Notes	ClinicalTrials.gov Last verified 2012. Confirmed by author 9 December 2015

Gesell 2004

Trial name or title	Hyperbaric Oxygen Therapy in Treating Patients with Radiation Necrosis of the Brain
Methods	RCT
Participants	People with radionecrosis of brain tissue
Interventions	HBOT, dexamethasone
Outcomes	Quality of life, lesion volume, oedema volume
Starting date	September 2003
Contact information	Gesell L; laurie.gesell@gmail.com

Gesell 2004 *(Continued)*

Notes	Continuing trial not confirmed

HOPON 2011

Trial name or title	Hyperbaric Oxygen for the Prevention of Osteoradionecrosis
Methods	RCT
Participants	People requiring surgery in an irradiated mandible
Interventions	HBOT
Outcomes	Prevention of ORN, mucosal healing at 6 months following surgery
Starting date	2010
Contact information	Binyam.Tesfaye@liverpool.ac.uk
Notes	Still recruiting. Confirmed by author 9 December 2015

Kuhnt 2008

Trial name or title	Hyperbaric Oxygen for the Treatment of a Dry Mouth Which Occurred After Radiotherapy
Methods	RCT
Participants	People with xerostomia
Interventions	HBOT
Outcomes	Change in saliva volume and xerostomia score
Starting date	May 2008
Contact information	Kuhnt T.; thomas.kuhnt@medizin.uni-halle.de
Notes	Not confirmed still recruiting

NCT01606644

Trial name or title	Hyperbaric Oxygen - a New Treatment Modality in Patients With Radiation Damaged Salivary Gland Tissue
Methods	Parallel Assignment, randomised clinical trial
Participants	18 Years and older (Adult, Older Adult) male and female
Interventions	Procedure: Hyperbaric oxygen. Inhalation of 100% oxygen for 90 minutes
Outcomes	Salivation rate; Quality of life; Xerostomia

NCT01606644 *(Continued)*

Starting date	May 2010
Contact information	Department of Anaesthesia and Department of Oral and Maxillofacial Surgery, Copenhagen University Hospital Lone Forner, DDS, PhD +45 3545 8211 lone.forner@rh.regionh.dk
Notes	Last Update Posted: May 28, 2012 Recruitment status unknown

NCT01822405

Trial name or title	Treatment of Radiation-induced Fibrosis in the Upper Aerodigestive Tract Cancer by a Combination of Pentoxifylline-tocopherol and Hyperbaric Oxygen (ORT-OXI-2009)
Methods	Parallel Assignment, randomised clinical trial
Participants	Patients with head and neck tumors
Interventions	pentoxifylline with tocopherol +- hyperbaric oxygen therapy
Outcomes	Change in skin fibrosis measured by MRI Clinical assessment of the radiation late (delayed) toxicity for mucosal membranes, salivary glands, larynx and skin by the LENT-SOMA scale (Late Effect Normal Tissue Task Force / Subjective, Objective, Management, Analytic scale) [Time Frame: Baseline and 6 months]
Starting date	July 2010
Contact information	Hospital Universitario de Canarias Claudio Oton coton@ull.es
Notes	Last Update Posted: April 2, 2013

NCT02425215

Trial name or title	HBOT Late Radiation Tissue Injury
Methods	Prospective observational study (n=300)
Participants	Patients that have had radiation therapy for malignancy, developed late radiation injury and suffer from chronic pain.18 Years and older
Interventions	
Outcomes	Pain Intensity Pain Disability Quality of Life Measurement

NCT02425215 *(Continued)*

	The Patient Global Impression of Change Depression and Anxiety Pain medications
Starting date	June 2014
Contact information	Rita Katznelson, University Health Network, Torontorita.katznelson@uhn.ca
Notes	Last Update Posted: April 6, 2018

NCT02450305

Trial name or title	Hyperbaric Oxygen and Its Effect on Radiation Induced Long Term Side Effects
Methods	Observational, case control prospective study
Participants	males and females age > 18 previous radiation therapy to the head and neck region at least one year from end of treatment
Interventions	
Outcomes	Xerostomia Taste alteration
Starting date	August 2013
Contact information	Marvin Heyboer, MD, State University of New York - Upstate Medical University
Notes	Last Update Posted: April 18, 2018

NCT02714465

Trial name or title	Adverse Radiation Effects After Gamma Knife Radio Surgery and Hyperbaric Oxygen Therapy (GKSHBO)
Methods	Single Group Assignment, interventional
Participants	Patients will be recruited on the basis of the presence of cerebral radionecrosis post gamma knife surgery, documented by both clinical examination (Rankin Scale) and instrumental imaging (MRI)
Interventions	hyperbaric oxygen therapy
Outcomes	Evaluation of clinical improvement Evaluation of the reduction of the extent of edema lesion documented by MRI Measurement of complications from hyperbaric oxygen therapy and their severity
Starting date	March 2016
Contact information	Simonetta Passarani, MD +39 02 6444 ext 4637

NCT02714465 *(Continued)*

	simonetta.passarani@ospedaleniguarda.it
Notes	Last Update Posted: June 27, 2018

NCT03144206

Trial name or title	Evaluation of Hyperbaric Oxygen Therapy on Wound Healing Following Management of Soft Tissue Sarcoma With Neo-Adjuvant Radiation and Surgical Resection
Methods	RCT
Participants	Patients with soft tissue sarcomas over 18 years
Interventions	Hyperbaric oxygen
Outcomes	Wound Complications Surgical site infections or periprosthetic infections Local wound management Reoperation due to wound complications
Starting date	October 2017
Contact information	Will Eward, Duke University, Northa Carolina william.eward@duke.edu
Notes	Last Update Posted: October 18, 2018

Oscarsson 2012

Trial name or title	Radiation Induced Cystitis Treated With Hyperbaric Oxygen - a Randomized Controlled Trial (RICH-ART)
Methods	RCT
Participants	People with radiation cystitis
Interventions	HBOT
Outcomes	Expanded Prostate Cancer Index Composite, 36-item Short Form, EORTC score
Starting date	August 2012
Contact information	Oscarsson N; nicklas.oscarsson@vgregion.se
Notes	Confirmed by author 9 December 2015

Yarnold 2010

Trial name or title	Randomized Double-Blind Controlled Phase III Trial of Hyperbaric Oxygen Therapy in Patients Suffering Long-Term Adverse Effects of Radiotherapy for Pelvic Cancer (HOT II)
Methods	RCT
Participants	Pelvic LRTI
Interventions	HBOT
Outcomes	Gastrointestinal symptoms score using the IBDQ quality-of-life questionnaire, LENT-SOMA
Starting date	January 2009
Contact information	John R. Yarnold, MD, FRCR, Royal Marsden Hospital
Notes	Not confirmed

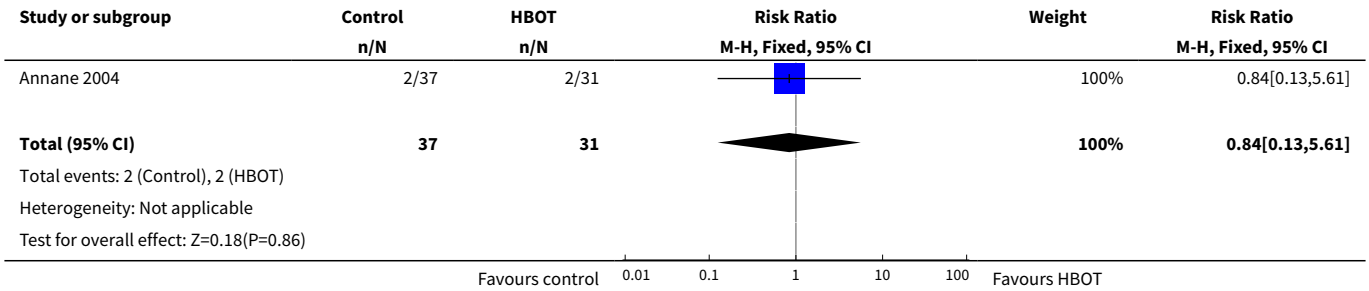
EORTC: European Organization for Research and Treatment of Cancer; HBOT: hyperbaric oxygen therapy; IBDQ: Inflammatory Bowel Disease Questionnaire; LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic; LRTI: late radiation tissue injury; ORN: osteoradionecrosis;
RCT: randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Death

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 1 year	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.13, 5.61]

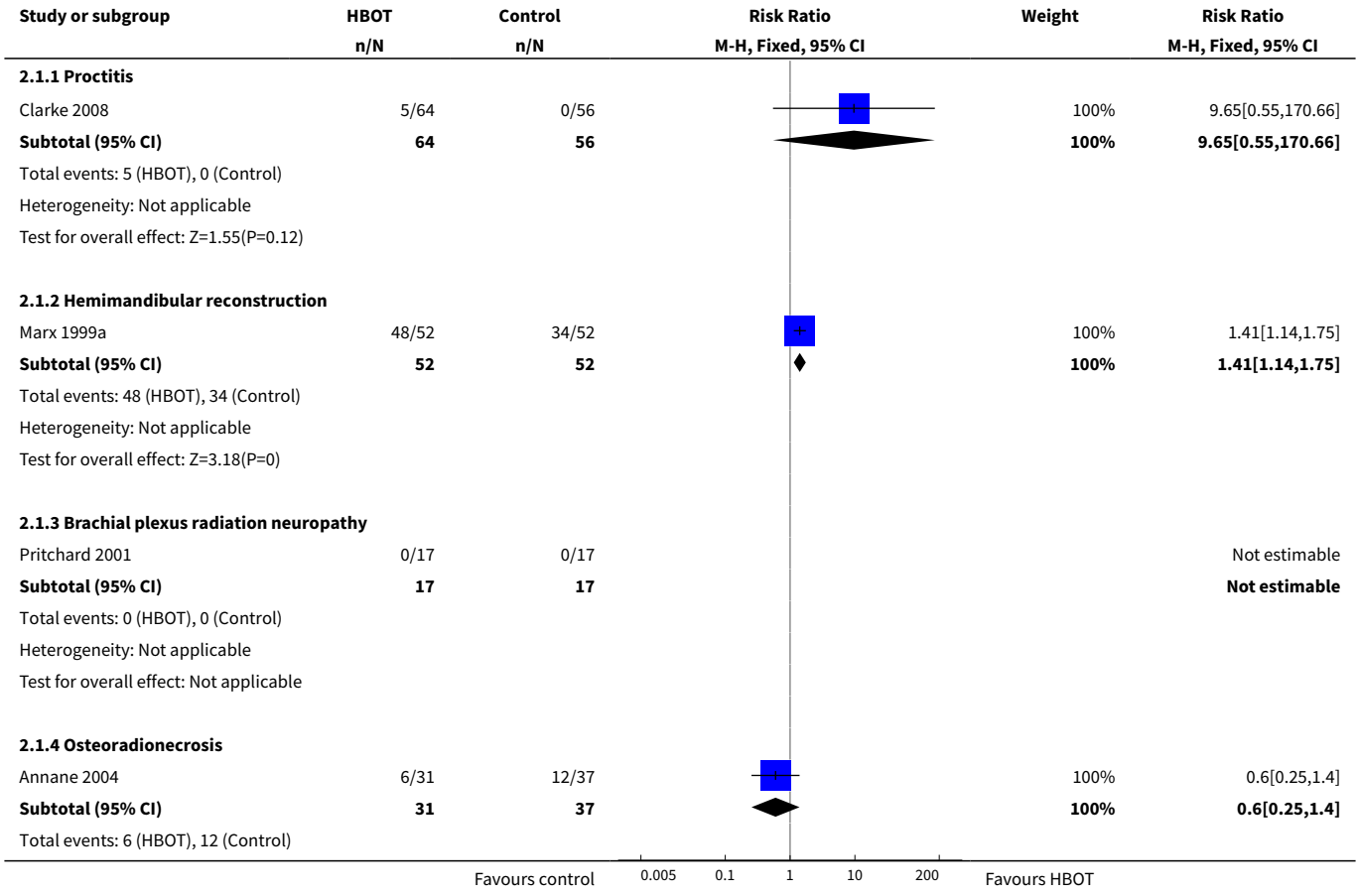
Analysis 1.1. Comparison 1 Death, Outcome 1 Death at 1 year.

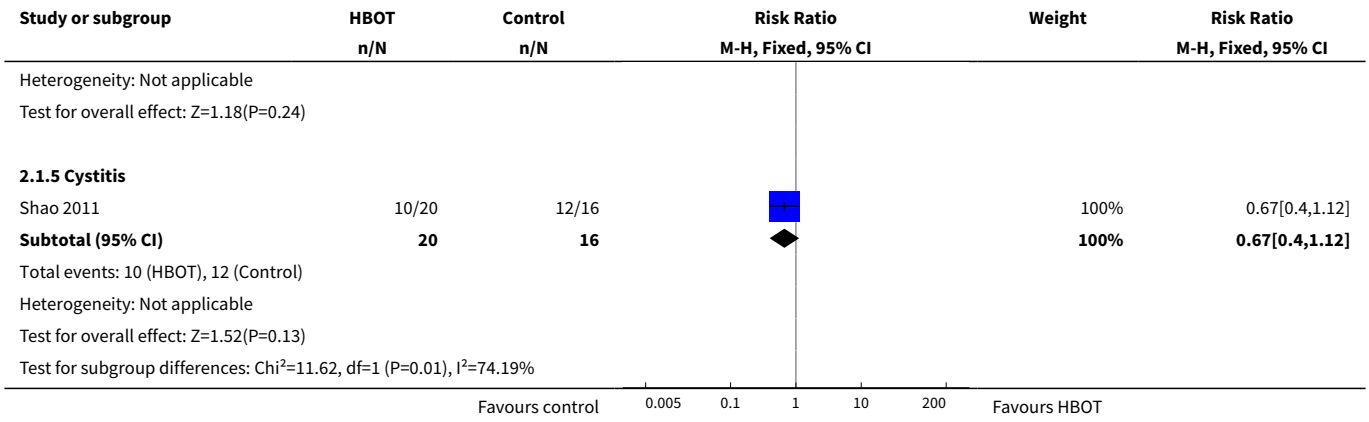


Comparison 2. Complete resolution of problem

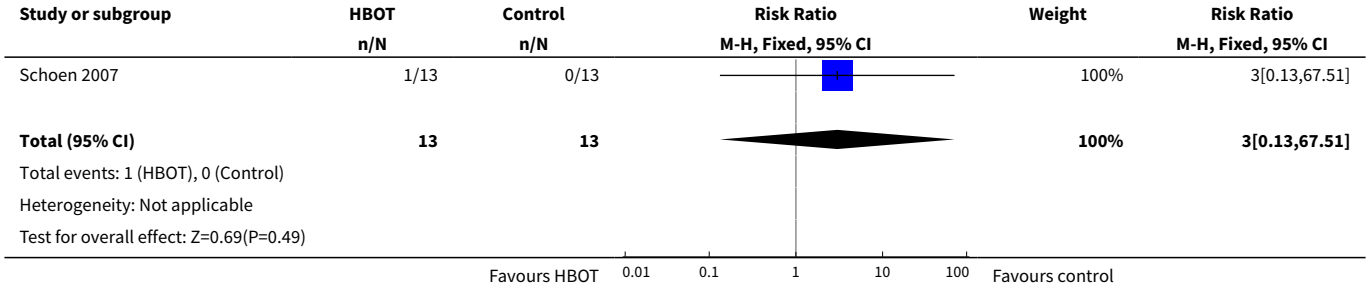
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of clinical problem at 1 year	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Proctitis	1	120	Risk Ratio (M-H, Fixed, 95% CI)	9.65 [0.55, 170.66]
1.2 Hemimandibular reconstruction	1	104	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.14, 1.75]
1.3 Brachial plexus radiation neuropathy	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Osteoradionecrosis	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.25, 1.40]
1.5 Cystitis	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.40, 1.12]
2 Development of osteoradionecrosis following dental implant	1	26	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 67.51]

Analysis 2.1. Comparison 2 Complete resolution of problem, Outcome 1 Resolution of clinical problem at 1 year.





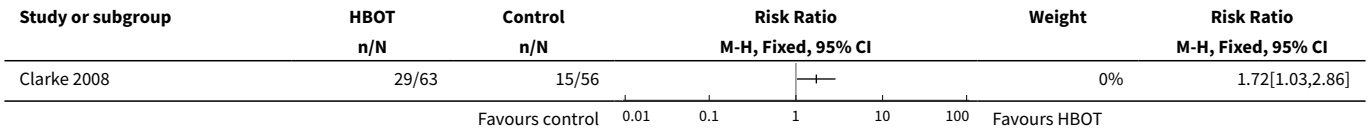
Analysis 2.2. Comparison 2 Complete resolution of problem, Outcome 2 Development of osteoradionecrosis following dental implant.

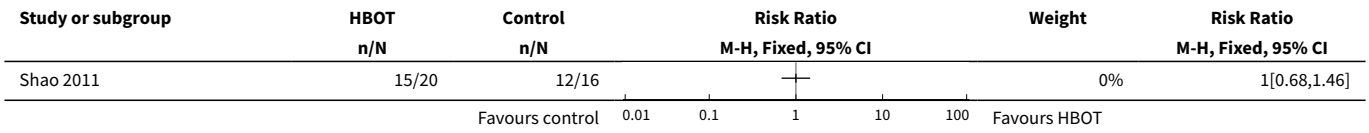


Comparison 3. Complete resolution or significant improvement of problem

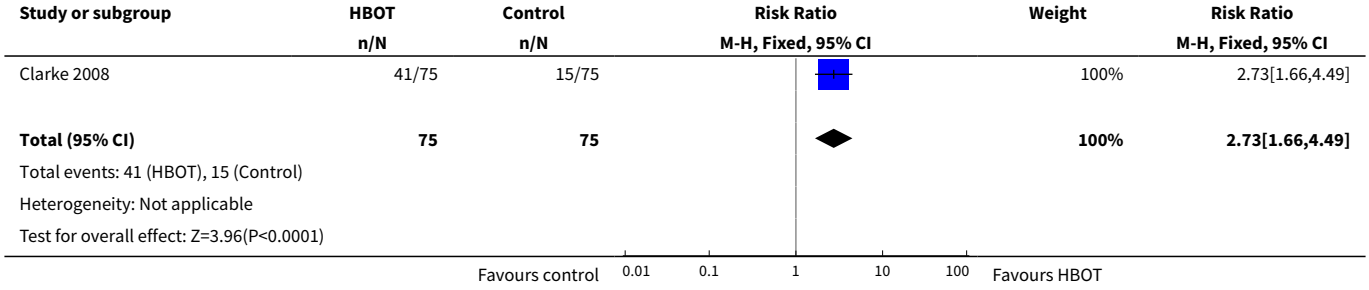
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete or significant improvement	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Sensitivity analysis for missing data in proctitis - best case	1	150	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [1.66, 4.49]
3 Sensitivity analysis for missing data proctitis - worst case	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.47, 0.93]

Analysis 3.1. Comparison 3 Complete resolution or significant improvement of problem, Outcome 1 Complete or significant improvement.

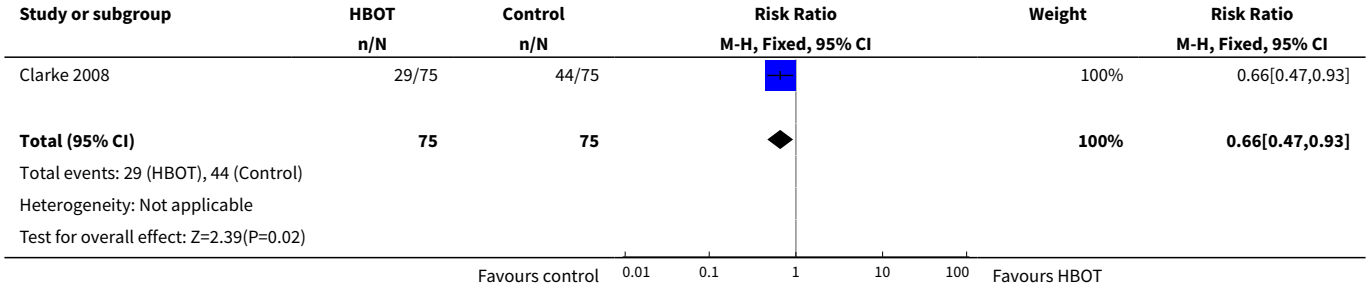




Analysis 3.2. Comparison 3 Complete resolution or significant improvement of problem, Outcome 2 Sensitivity analysis for missing data in proctitis - best case.



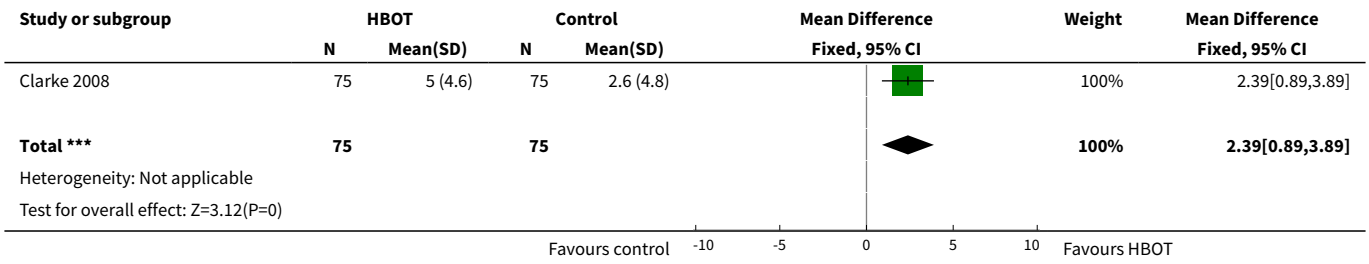
Analysis 3.3. Comparison 3 Complete resolution or significant improvement of problem, Outcome 3 Sensitivity analysis for missing data proctitis - worst case.



Comparison 4. Improvement in mean LENT-SOMA score

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean LENT-SOMA score at 3 months	1	150	Mean Difference (IV, Fixed, 95% CI)	2.39 [0.89, 3.89]

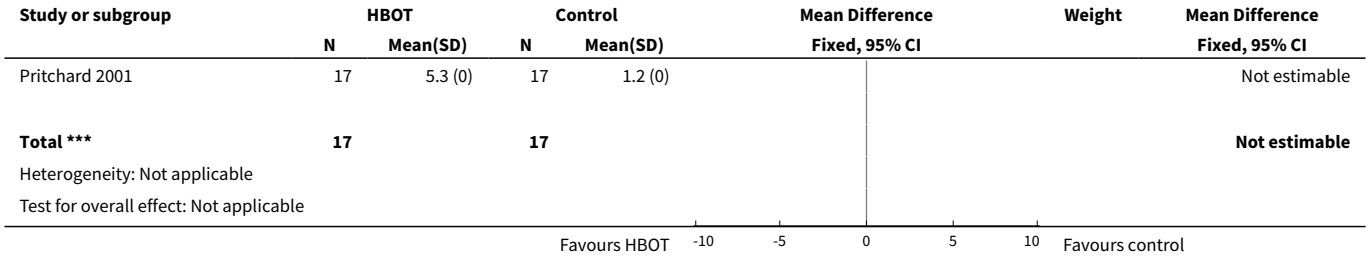
Analysis 4.1. Comparison 4 Improvement in mean LENT-SOMA score, Outcome 1 Mean LENT-SOMA score at 3 months.



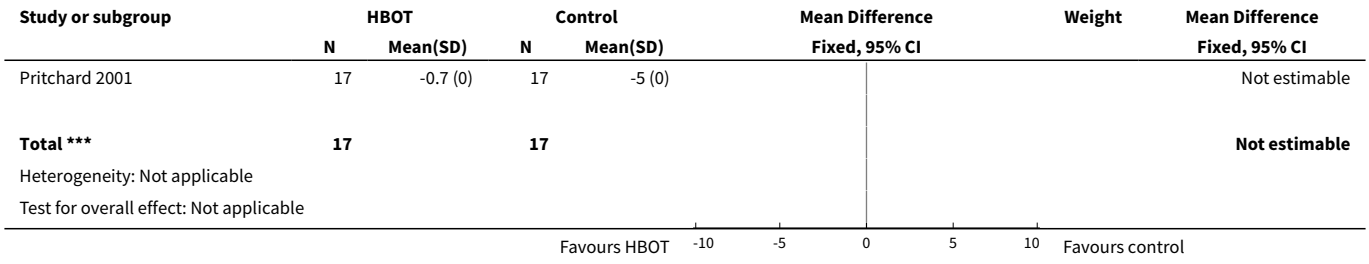
Comparison 5. Resolution of pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score change at end of treatment	1	34	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Pain score change at 12 months	1	34	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Pain score change at 18 months	1	36	Mean Difference (IV, Fixed, 95% CI)	3.5 [-4.48, 11.48]

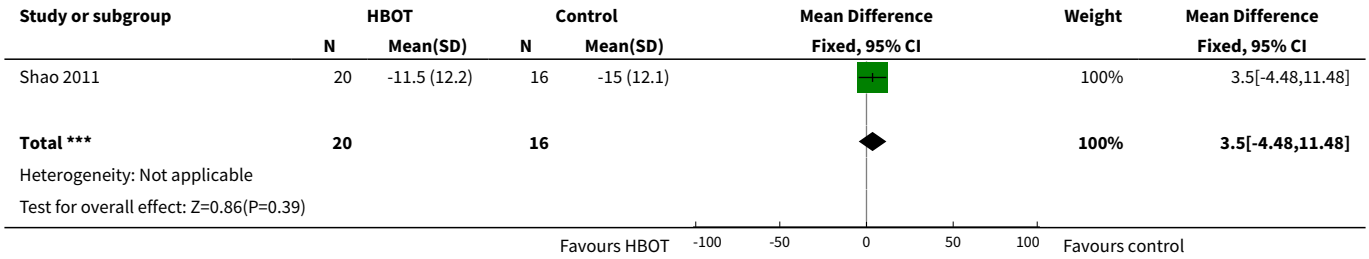
Analysis 5.1. Comparison 5 Resolution of pain, Outcome 1 Pain score change at end of treatment.



Analysis 5.2. Comparison 5 Resolution of pain, Outcome 2 Pain score change at 12 months.



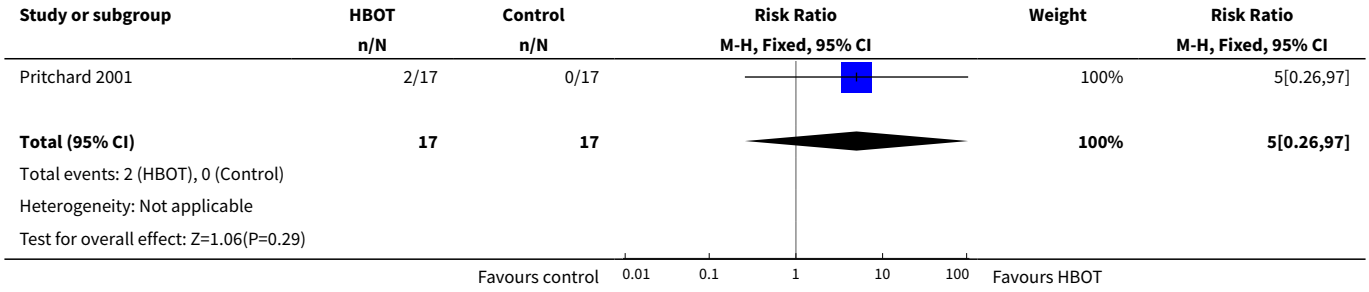
Analysis 5.3. Comparison 5 Resolution of pain, Outcome 3 Pain score change at 18 months.



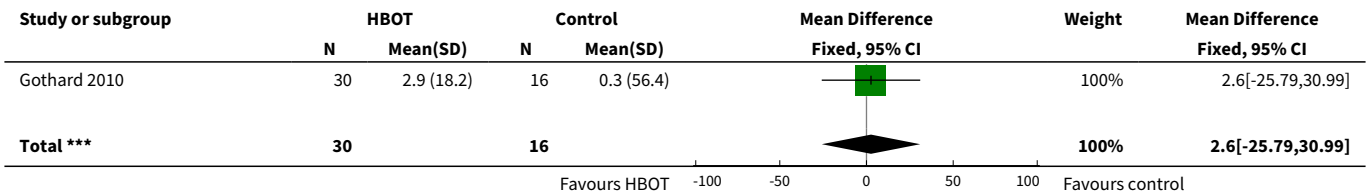
Comparison 6. Resolution of swelling

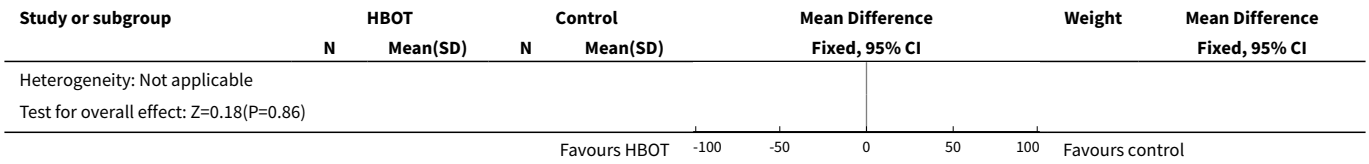
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement of lymphoedema	1	34	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 97.00]
2 Relative reduction in arm volume (affected vs. non-affected)	1	46	Mean Difference (IV, Fixed, 95% CI)	2.6 [-25.79, 30.99]
3 Proportion with more than 8% reduction in arm volume	1	46	Odds Ratio (M-H, Fixed, 95% CI)	1.86 [0.42, 8.15]

Analysis 6.1. Comparison 6 Resolution of swelling, Outcome 1 Improvement of lymphoedema.

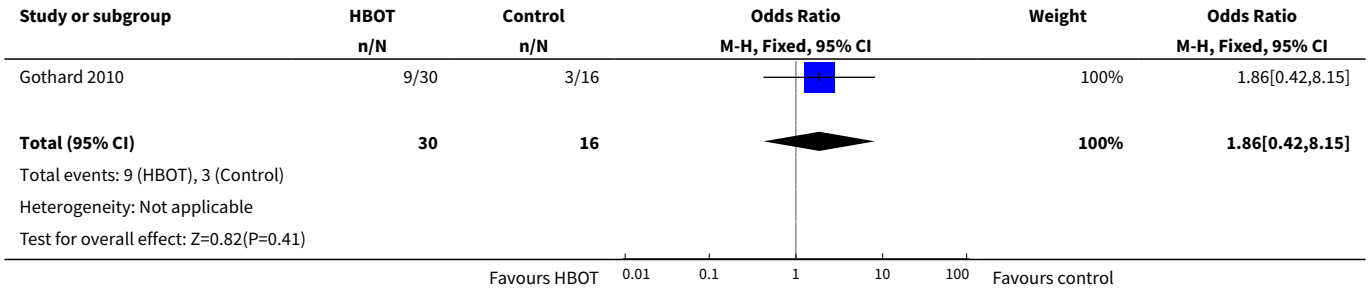


Analysis 6.2. Comparison 6 Resolution of swelling, Outcome 2 Relative reduction in arm volume (affected vs. non-affected).





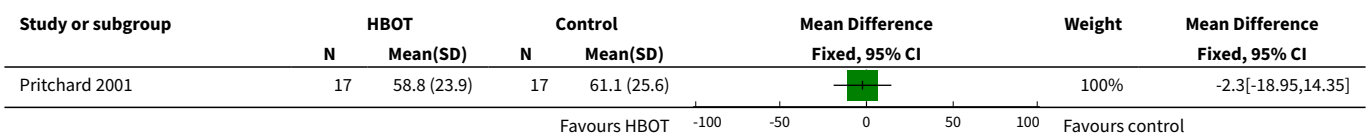
Analysis 6.3. Comparison 6 Resolution of swelling, Outcome 3 Proportion with more than 8% reduction in arm volume.

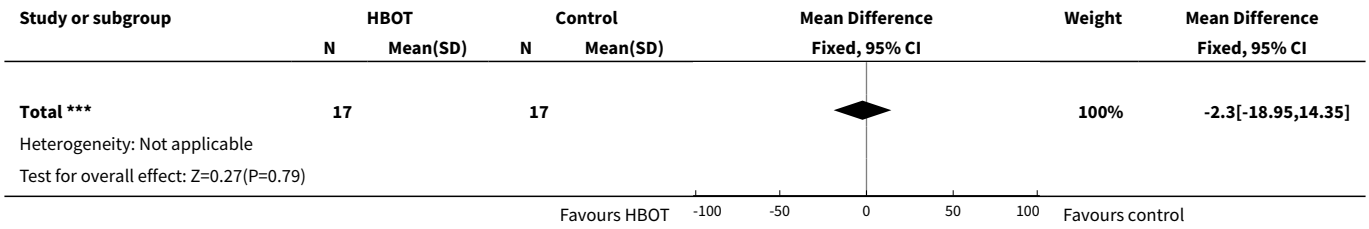


Comparison 7. Quality of life and functional outcomes

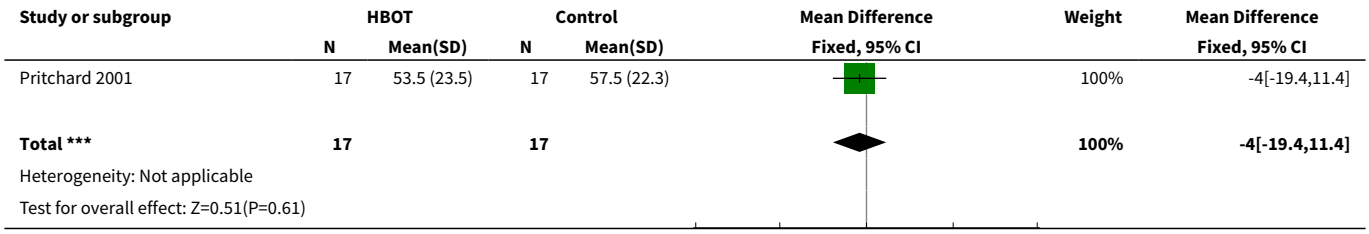
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SF-36 general health at 1 year	1	34	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-18.95, 14.35]
2 Physical functioning score at 1 year	1	34	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-19.40, 11.40]
3 Improvements in mean bowel bother score	1	150	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Lymphoedema score at 12 months	1	58	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Quality of life (EORTC Head and Neck Module) at 12 months	1	19	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Quality of Life (EORTC Head and Neck Module) at 12 months	1	26	Mean Difference (IV, Fixed, 95% CI)	-17.60 [-30.61, -4.59]

Analysis 7.1. Comparison 7 Quality of life and functional outcomes, Outcome 1 SF-36 general health at 1 year.

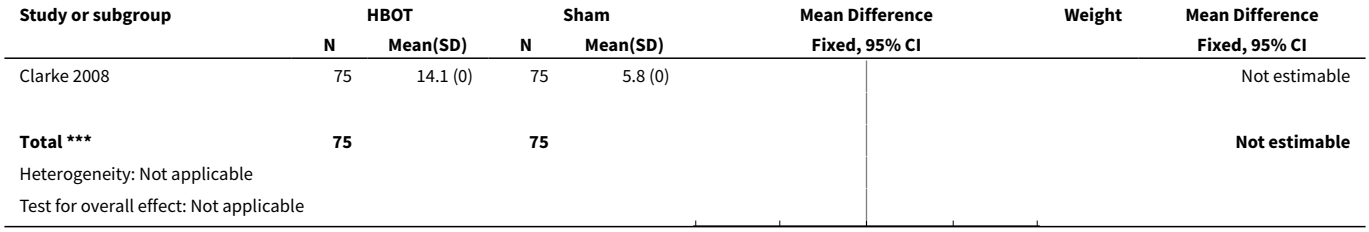




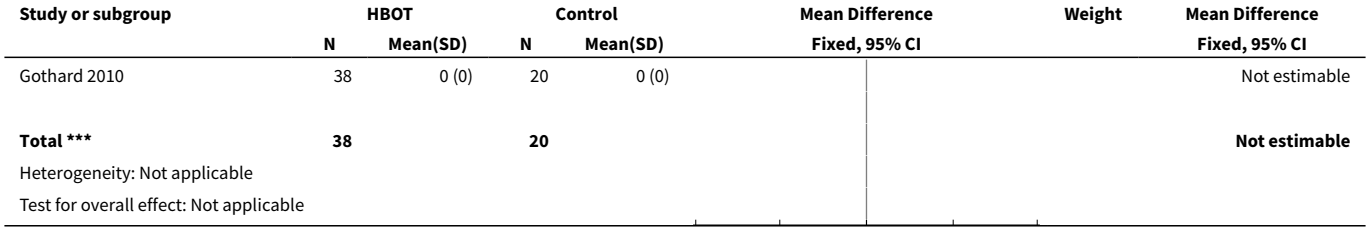
Analysis 7.2. Comparison 7 Quality of life and functional outcomes, Outcome 2 Physical functioning score at 1 year.



Analysis 7.3. Comparison 7 Quality of life and functional outcomes, Outcome 3 Improvements in mean bowel bother score.



Analysis 7.4. Comparison 7 Quality of life and functional outcomes, Outcome 4 Lymphoedema score at 12 months.

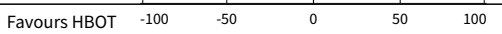


Analysis 7.5. Comparison 7 Quality of life and functional outcomes, Outcome 5 Quality of life (EORTC Head and Neck Module) at 12 months.

Study or subgroup	HBOT N	HBOT Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Teguh 2009	8	25 (0)	11	62 (0)			Not estimable
Total ***	**8**		**11**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Analysis 7.6. Comparison 7 Quality of life and functional outcomes, Outcome 6 Quality of Life (EORTC Head and Neck Module) at 12 months.

Study or subgroup	HBOT N	HBOT Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Schoen 2007	13	66.7 (13.6)	13	84.3 (19.7)		100%	-17.6[-30.61,-4.59]
Total ***	**13**		**13**			**100%**	**-17.6[-30.61,-4.59]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.65(P=0.01)							

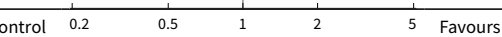


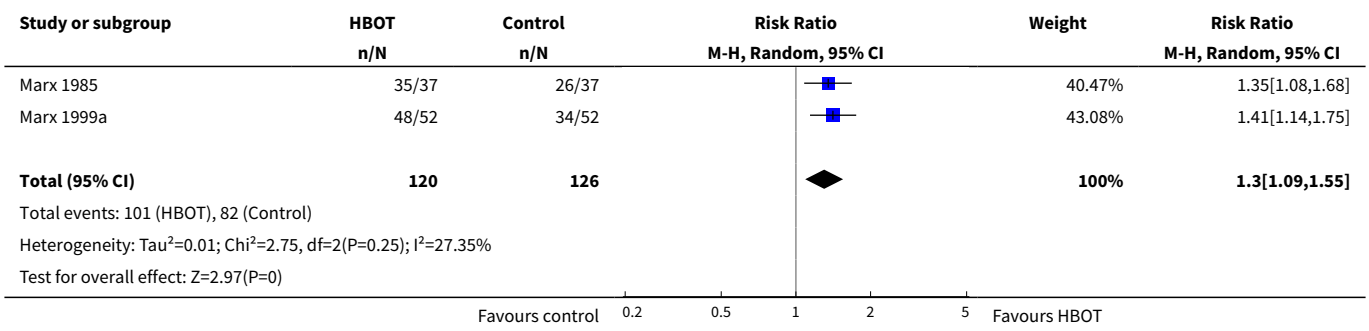
Comparison 8. Osteoradionecrosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete mucosal cover	3	246	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.09, 1.55]
2 Establishment of bony continuity	1	104	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.14, 1.75]
3 Resolution of sinus tract	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Successful healing of tooth sockets after tooth extraction	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.08, 1.68]
5 Bone loss around implant site	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.67, 0.47]

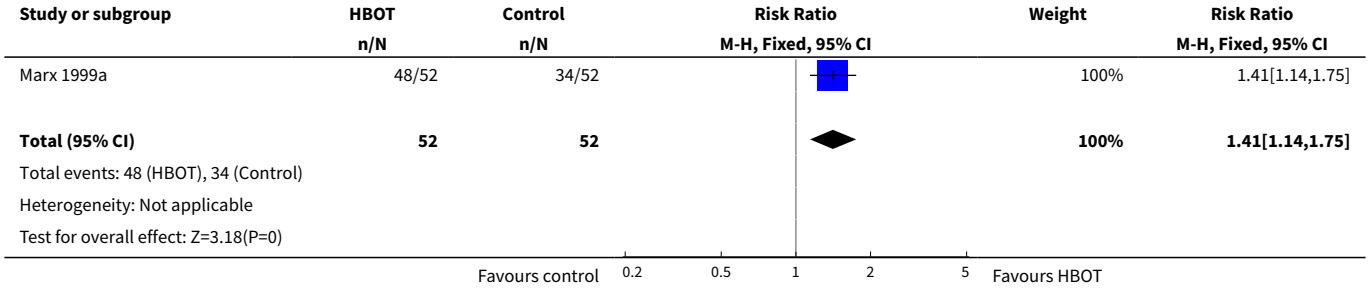
Analysis 8.1. Comparison 8 Osteoradionecrosis, Outcome 1 Complete mucosal cover.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Annane 2004	18/31	22/37		16.45%	0.98[0.65,1.46]

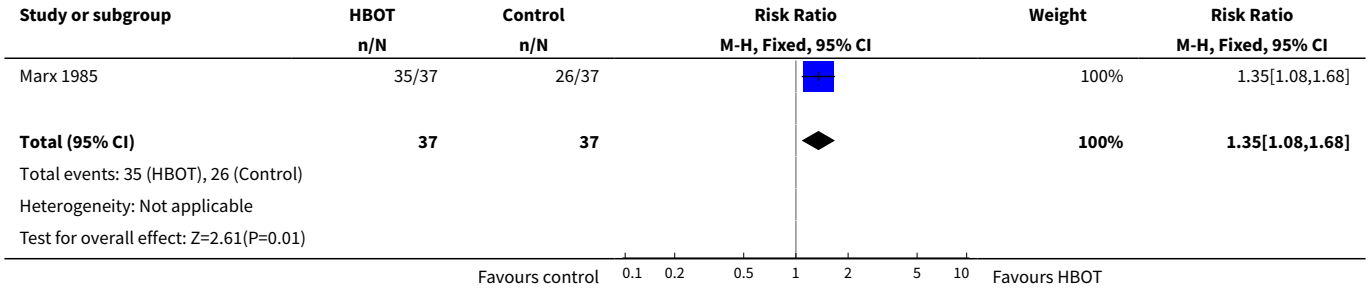




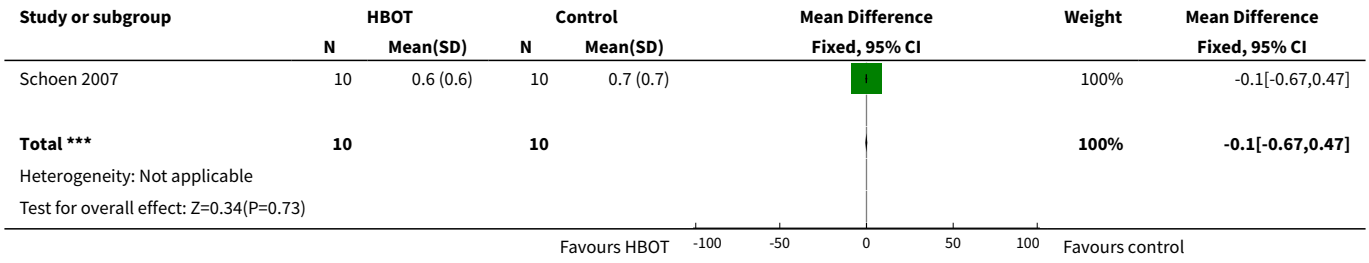
Analysis 8.2. Comparison 8 Osteoradionecrosis, Outcome 2 Establishment of bony continuity.



Analysis 8.4. Comparison 8 Osteoradionecrosis, Outcome 4 Successful healing of tooth sockets after tooth extraction.



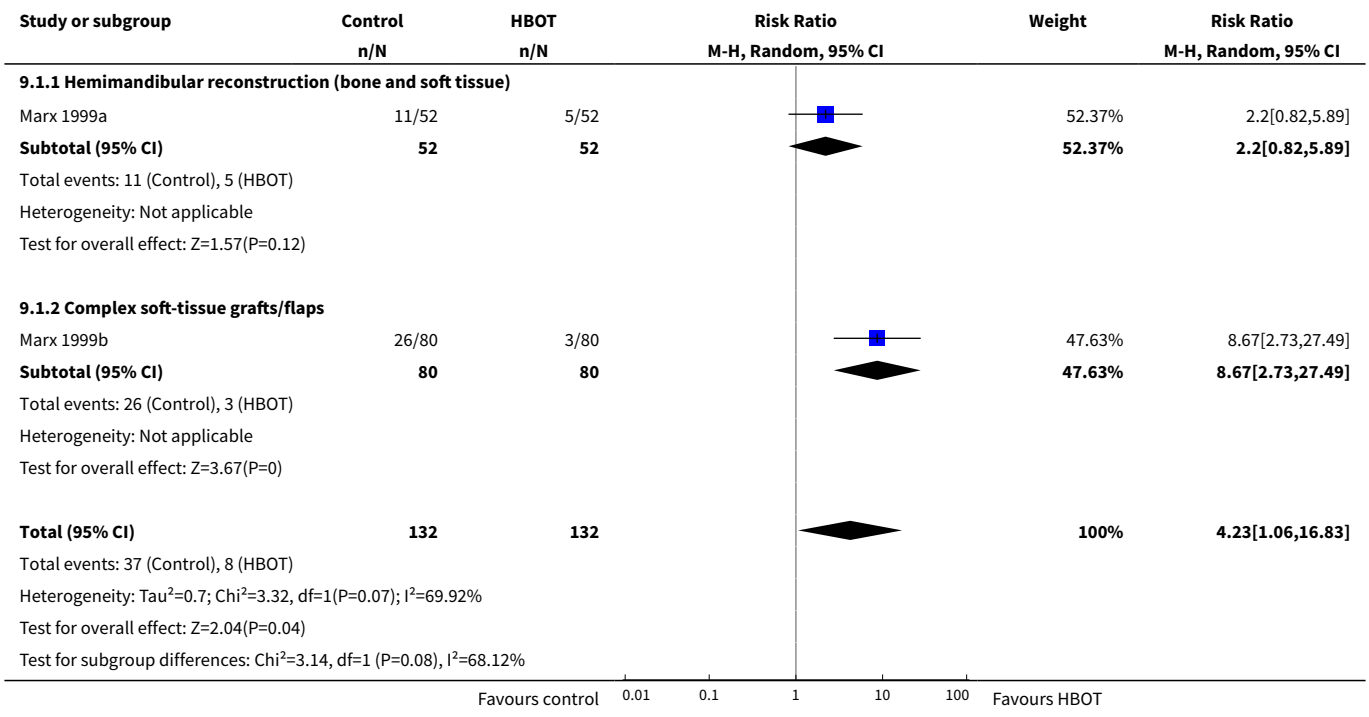
Analysis 8.5. Comparison 8 Osteoradionecrosis, Outcome 5 Bone loss around implant site.



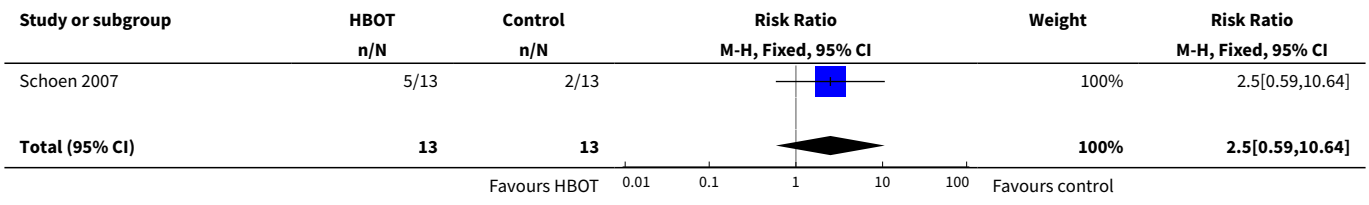
Comparison 9. Head and neck soft tissues

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Wound dehiscence	2	264	Risk Ratio (M-H, Random, 95% CI)	4.23 [1.06, 16.83]
1.1 Hemimandibular reconstruction (bone and soft tissue)	1	104	Risk Ratio (M-H, Random, 95% CI)	2.2 [0.82, 5.89]
1.2 Complex soft-tissue grafts/flaps	1	160	Risk Ratio (M-H, Random, 95% CI)	8.67 [2.73, 27.49]
2 Loss of dental implant	1	26	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.59, 10.64]

Analysis 9.1. Comparison 9 Head and neck soft tissues, Outcome 1 Wound dehiscence.



Analysis 9.2. Comparison 9 Head and neck soft tissues, Outcome 2 Loss of dental implant.



Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 5 (HBOT), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.24(P=0.22)					

Comparison 10. Urinary bladder

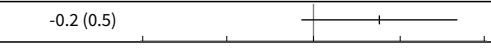
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete resolution of clinical problem	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.45, 1.79]
2 Removal of bladder or urinary diversion	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Daily voiding frequency change at 18 months	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Analysis 10.1. Comparison 10 Urinary bladder, Outcome 1 Complete resolution of clinical problem.

Study or subgroup	HBOT n/N	Hyaluronidase n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Shao 2011	9/20	8/16		100%	0.9[0.45,1.79]
Total (95% CI)	**20**	**16**		**100%**	**0.9[0.45,1.79]**
Total events: 9 (HBOT), 8 (Hyaluronidase)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.3(P=0.76)					

Analysis 10.3. Comparison 10 Urinary bladder, Outcome 3 Daily voiding frequency change at 18 months.

Study or subgroup	HBOT N	HBOT Mean(SD)	Hyaluronidase N	Hyaluronidase Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Shao 2011	20	0.2 (0.8)	16	-0.2 (0.5)		0%	0.38[-0.07,0.83]

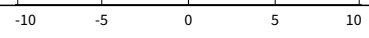


Comparison 13. Neurological tissue

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Warm sensory threshold 1 week after treatment (°C change from baseline)	1	34	Mean Difference (IV, Fixed, 95% CI)	1.12 [-1.90, 4.14]
2 Warm sensory threshold at 1 year	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.87 [-3.97, 2.23]
3 Net number of significantly improved neuropsychological tests at 3 months (25 tests total)	1	7	Mean Difference (IV, Fixed, 95% CI)	2.00 [-1.60, 5.60]
4 Net number of significantly improved neuropsychiatric tests at 6 months	1	7	Mean Difference (IV, Fixed, 95% CI)	1.0 [-3.55, 5.55]

Analysis 13.1. Comparison 13 Neurological tissue, Outcome 1 Warm sensory threshold 1 week after treatment (°C change from baseline).

Study or subgroup	Control N	Control Mean(SD)	HBOT N	HBOT Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Pritchard 2001	17	1 (3.9)	17	-0.1 (5)		100%	1.12[-1.9,4.14]
Total ***	**17**		**17**			**100%**	**1.12[-1.9,4.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.73(P=0.47)							

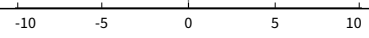


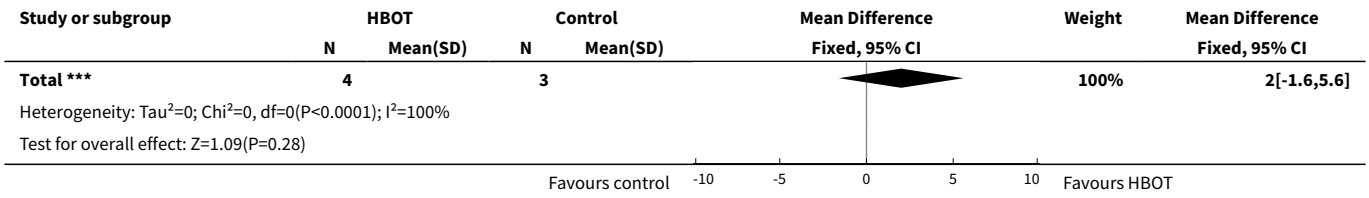
Analysis 13.2. Comparison 13 Neurological tissue, Outcome 2 Warm sensory threshold at 1 year.

Study or subgroup	Control N	Control Mean(SD)	HBOT N	HBOT Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Pritchard 2001	17	0.5 (3.4)	17	1.4 (5.5)		100%	-0.87[-3.97,2.23]
Total ***	**17**		**17**			**100%**	**-0.87[-3.97,2.23]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.55(P=0.58)							

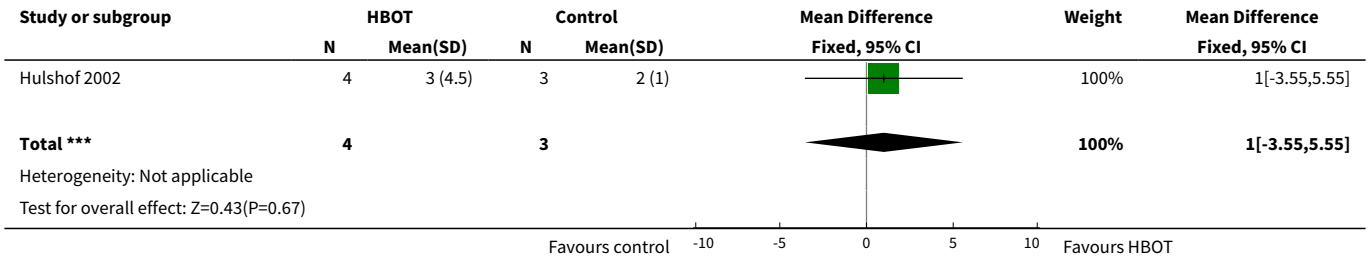
Analysis 13.3. Comparison 13 Neurological tissue, Outcome 3 Net number of significantly improved neuropsychological tests at 3 months (25 tests total).

Study or subgroup	HBOT N	HBOT Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hulshof 2002	4	3.3 (3.4)	3	1.3 (1.2)		100%	2[-1.6,5.6]





Analysis 13.4. Comparison 13 Neurological tissue, Outcome 4 Net number of significantly improved neuropsychiatric tests at 6 months.



ADDITIONAL TABLES

Table 1. The LENT-SOMA Scales - conceptual summary

(S)ubjective	(O)bjective	(M)edical management	(A)nalytic
The injury from the person's point of view. May involve interview, diary or questionnaire depending on the system to be used	Morbidity assessed objectively by clinician during physical examination	The active steps that have been taken in order to ameliorate the symptoms	Diagnostic and imaging tools used to further objectively define the level of injury

APPENDICES

Appendix 1. 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)

Appendix 2. MEDLINE search strategy (via Ovid)

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:

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 3. 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 4. CINAHL search strategy

1. exp radiation injuries/
2. RADIOTHERAPY/ae
3. (radiation or radiother*).mp.
4. (damage* or injur* of wound* or destruction or oedema or edema or fracture*).mp.
5. 4 and 3
6. 1 or 2 or 5
7. exp hyperbaric oxygenation/
8. (high adj3 pressure).mp.
9. (high adj3 tension).mp.
10. (hyperbaric and oxygen$).mp.
11. (HBO or HBOT).mp.
12. (multiplace chamber$ or multiplace hyperbaric chamber$).mp.
13. (monoplace chamber$ or monoplace hyperbaric chamber$).mp.
14. 8 or 11 or 7 or 13 or 10 or 9 or 12
15. 6 and 14
16. exp Clinical Trials/
17. (randomized or controlled).mp.
18. 16 and 17
19. randomized controlled trial.mp.
20. controlled clinical trial.mp.
21. randomized.ti,ab.
22. randomly.ti,ab.
23. trial.ti,ab.
24. groups.ti,ab.
25. 22 or 21 or 18 or 24 or 23 or 19 or 20
26. Animals/
27. (man or woman or human being).mp.
28. 26 not (26 and 27)
29. 25 not 28
30. 29 and 15

Appendix 5. DORCTIHM search strategy

1. Radiotherapy OR radiation tissue injury OR late radiation effect

WHAT'S NEW

Date	Event	Description
31 October 2018	Amended	Review not for update until ongoing studies completed.

HISTORY

Protocol first published: Issue 2, 2004
Review first published: Issue 3, 2005

Date	Event	Description
9 March 2016	New citation required but conclusions have not changed	The current update includes substantial changes in presentation and content, but the conclusions are unchanged.
9 March 2016	New search has been performed	The review has been update. Specifically we have:

Date	Event	Description
		Added three further trials. Amended text of abstract, results and discussion to reflect the new material. Updated discussion to include more contemporary references. Updated the study flow diagram. Re-formatted and updated the summary of findings table. Re-formatted the results section, removed text references to single trial analyses and replaced with results from the original papers. We deleted the sensitivity analyses for single trials.
29 March 2012	New citation required but conclusions have not changed	Searches re-run March 2011 and three new studies identified.
11 January 2012	New search has been performed	'Risk of bias' and 'Summary of findings' tables added. Study flow figure added. No major change to conclusions
23 August 2008	New search has been performed	Two new trials identified and added to review when searches were re-run in August 2008.
26 April 2008	Amended	Converted to new review format.
23 May 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.
John Feldmeier: co-author, data extraction and critical appraisal, radiation oncology and hyperbaric medicine content expert.
Neil Hampson: co-author, editorial advice, data extraction and critical appraisal, hyperbaric medicine content expert.
Robert Smee: editorial advice, radiation oncology content expert.
Chris Milross: co-author, background, radiation oncology content expert.

DECLARATIONS OF INTEREST

None known. Bennett and Hampson are hyperbaric physicians who regularly treat people with LRTI, while Feldmeier has previous hyperbaric experience. Milross, Feldmeier and Smee are radiation oncologists who refer people with LRTI for HBOT.

SOURCES OF SUPPORT

Internal sources

- No source of support, Other.

External sources

- No external source of support, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We amended the secondary outcome of quality of life to include any scale designed to measure quality of life or functional ability.

INDEX TERMS

Medical Subject Headings (MeSH)

Anus Neoplasms [radiotherapy]; Head and Neck Neoplasms [radiotherapy]; Hyperbaric Oxygenation [*methods]; Neoplasms [*radiotherapy]; Organs at Risk [radiation effects]; Osteoradionecrosis [prevention & control]; Radiation Injuries [prevention & control] [*therapy]; Randomized Controlled Trials as Topic; Rectal Neoplasms [radiotherapy]

MeSH check words

Humans