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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

This is the third update of the original Cochrane Review published in July 2005 and updated previously in 2012 and 2016.

Cancer is a significant global health issue. Radiotherapy is a treatment modality for many malignancies, and about 50% of people having radiotherapy will be long-term survivors. Some will experience late radiation tissue injury (LRTI), developing months or years following radiotherapy. Hyperbaric oxygen therapy (HBOT) has been suggested as a treatment for LRTI based on 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 complications following surgery and radiotherapy.

Objectives

To evaluate the benefits and harms of hyperbaric oxygen therapy (HBOT) for treating or preventing late radiation tissue injury (LRTI) compared to regimens that excluded HBOT.

Search methods

We used standard, extensive Cochrane search methods. The latest search date was 24 January 2022.

Selection criteria

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

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were 1. survival from time of randomisation to death from any cause; 2. complete or substantial resolution of clinical problem; 3. site-specific outcomes; and 4. adverse events. Our secondary outcomes were 5. resolution of pain; 6. improvement in quality of life, function, or both; and 7. site-specific outcomes. We used GRADE to assess certainty of evidence.

Main results

Eighteen studies contributed to this review (1071 participants) with publications ranging from 1985 to 2022. We added four new studies to this updated review and evidence for the treatment of radiation proctitis, radiation cystitis, and the prevention and treatment of osteoradionecrosis (ORN).

HBOT may not prevent death at one year (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.47 to 1.83; I^2 = 0%; 3 RCTs, 166 participants; low-certainty evidence). There is some evidence that HBOT may result in complete resolution or provide significant improvement of LRTI (RR 1.39, 95% CI 1.02 to 1.89; I^2 = 64%; 5 RCTs, 468 participants; low-certainty evidence) and HBOT may result in a large reduction in wound dehiscence following head and neck soft tissue surgery (RR 0.24, 95% CI 0.06 to 0.94; I^2 = 70%; 2 RCTs, 264 participants; low-certainty evidence). In addition, pain scores in ORN improve slightly after HBOT at 12 months (mean difference (MD) −10.72, 95% CI −18.97 to −2.47; I^2 = 40%; 2 RCTs, 157 participants; moderate-certainty evidence).

Regarding adverse events, HBOT results in a higher risk of a reduction in visual acuity (RR 4.03, 95% CI 1.65 to 9.84; 5 RCTs, 438 participants; high-certainty evidence). There was a risk of ear barotrauma in people receiving HBOT when no sham pressurisation was used for the control group (RR 9.08, 95% CI 2.21 to 37.26; I^2 = 0%; 4 RCTs, 357 participants; high-certainty evidence), but no such increase when a sham pressurisation was employed (RR 1.07, 95% CI 0.52 to 2.21; I^2 = 74%; 2 RCTs, 158 participants; high-certainty evidence).

Authors' conclusions

These small studies suggest that for people with LRTI affecting tissues of the head, neck, bladder and rectum, HBOT may be associated with improved outcomes (low- to moderate-certainty evidence). HBOT may also result in a reduced risk of wound dehiscence and a modest reduction in pain following head and neck irradiation. However, HBOT is unlikely to influence the risk of death in the short term. HBOT also carries a risk of adverse events, including an increased risk of a reduction in visual acuity (usually temporary) and of ear barotrauma on compression. Hence, the application of HBOT to selected participants may be justified.

The small number of studies and participants, and the methodological and reporting inadequacies of some of the primary studies included in this review demand a cautious interpretation. 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 most appropriate oxygen dose. Further research is required to establish the optimum participant selection and timing of any therapy. An economic evaluation should also be undertaken.

PLAIN LANGUAGE SUMMARY

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

Key message

– In selected people and areas of the body hyperbaric oxygen therapy (HBOT) may help resolve symptoms associated with late radiation tissue injury (LRTI) but further research is required to establish which people may respond and the best timing of such therapy.

What are the problems after radiation treatment and how can it be treated?

There is a risk of serious complications developing in the months and years after radiation treatment (radiotherapy) for cancer. These problems are collectively called LRTI and are due to progressive damage to normal tissue (cells within the body) that has been exposed to radiation. These problems can be very difficult to resolve, and there is some doubt as to the best approaches to treatment. HBOT involves breathing oxygen in a specially designed pressurised chamber. It is used to improve oxygen supply to damaged tissue and support healing.

What did we want to find out?

We wanted to find out if HBOT results in both healing of tissues and the prevention of complications following surgery in an irradiated field and radiotherapy for cancer.

What did we do?

We searched medical databases for clinical studies reporting the evidence for or against the ability of HBOT to improve these complications compared to either no treatment or alternative treatments.

What were the main findings?

There was some evidence that HBOT may improve outcomes in LRTI affecting both bone and soft tissues of the head and neck, the bladder and the lower bowel. There was also some evidence that HBOT may reduce wound breakdown and improve pain following LRTI. HBOT did not affect the risk of dying over the short time that these studies followed their patients. HBOT is generally safe and well-tolerated, but there is a risk of becoming temporarily short-sighted from the oxygen exposure and of injury to the ear drum on compression.

What are the limitations of the evidence?

The evidence was mainly limited by small numbers of people and studies, poor reporting of methods and results, and uncertainty as to the exact degree of improvement with HBOT. A study of costs would also be useful.

How up to date is this evidence?

The evidence is current to January 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Hyperbaric oxygen therapy (HBOT) compared to control without HBOT for late radiation tissue injury of any tissue

Patient or population: any person with radiation tissue injury arising later than 6 months after irradiation (LRTI), including dysfunction or necrosis of any tissue
Setting: outpatient or hospital
Intervention: HBOT
Comparison: any approach not including HBOT

Outcomes	Anticipated absolute effects* (95% CI)			№ of participants (studies)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	What happens
	Without HBOT	With HBOT	Difference				
Death at 1 year	**Study population**			166 (3 RCTs)	**RR 0.93** (0.47 to 1.83)	⊕⊕⊖⊖ **Low**[a,b]	Although 4 studies reported deaths, only 3 contributed to this analysis. There was no evidence of a difference death at 1 year between groups.
	16.7%	15.5% (7.8% to 30.5%)	**1.2% less** (8.8% less to 13.8% more)				
Complete or substantial improvement of condition	**Study population**			468 (6 RCTs)	**RR 1.39** (1.02 to 1.89)	⊕⊕⊖⊖ **Low**[c]	This analysis includes 3 different tissue types. 1 study compared HBOT to another intervention whilst 4 studies compared HBOT to control without HBOT and there may be further important clinical heterogeneity that was not evident. The use of HBOT may result in an increased proportion of people with substantial improvement in symptoms. These results suggest we need to treat 8 people to achieve complete recovery or significant improvement of symptoms in 1 extra person.
	39.2%	54.5% (40% to 74.1%)	**15.3% more** (0.8% more to 34.9% more)				
Visual disturbances	**Study population**			438 (5 RCTs)	**RR 4.03** (1.65 to 9.84)	⊕⊕⊕⊕ **High**	HBOT results in a reduction in visual acuity at the end of treatment.[d]
	1.5%	6.2% (2.5% to 15.1%)	**4.7% more** (1% more to 13.6% more)				
Otic barotrauma	Absolute effects not calculated as 0 events in the control group			357 (4 RCTs)	**RR 9.08** (2.21 to 37.26)	⊕⊕⊕⊕ **High**	HBOT results in a large increase in otic barotrauma based on 4 studies.[d]

*__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; **HBOT:** hyperbaric oxygen therapy; **LRTI:** late radiation tissue injury; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level for imprecision due to wide confidence intervals.
[b] Downgraded one level as Sidik 2007 was at high risk of bias for poor reporting of randomisation and was not blinded.
[c] Downgraded one level as two studies had unclear methodology and serious risk of bias for reported outcomes (Marx 1999a; Shao 2011). Further downgraded by one level as there were high attrition rates in the osteoradionecrosis populations making the estimate less certain.
[d] Consistent with expected incidence from historical reviews.

Summary of findings 2. Hyperbaric oxygen therapy (HBOT) compared to control without HBOT for prevention or treatment of osteoradionecrosis of the mandible or maxilla

Patient or population: any person with osteoradionecrosis of the jaw or at risk of osteoradionecrosis of the jaw
Setting: outpatient or hospital
Intervention: HBOT
Comparison: control without HBOT

Outcomes	Anticipated absolute effects* (95% CI)			№ of participants (studies)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	What happens
	Without HBOT	With HBOT	Difference				
Wound dehiscence	**Study population**			264 (2 RCTs)	**RR 0.24** (0.06 to 0.94)	⊕⊕⊝⊝ **Low**[a,b]	2 small studies found that HBOT may result in a reduction in the risk of wound dehiscence following operative treatment for osteoradionecrosis. This analysis suggests we would need to treat about 4 cases with adjunctive HBOT to avoid 1 extra case of dehiscence, but this estimate is imprecise.
	28.0%	6.7% (1.7% to 26.3%)	21.3% less (26.3 less to 1.7 less)				
Pain score change at 12 months	—	—	**MD 10.72 lower** (18.97 lower to 2.47 lower)	157 (2 RCTs)	—	⊕⊕⊕⊝ **Moderate**[a]	2 studies found that HBOT reduces pain slightly for osteoradionecrosis at 12 months.

Complete resolution or significant improvement of osteoradionecrosis	**Study population**			239 (3 RCTs)	**RR 1.26** (0.87 to 1.82)	⊕⊕⊖⊖ **Low**[c]	3 studies suggest that HBOT may result in little to no difference in the improvement of osteoradionecrosis.
	50.8%	64.0 (44.2% to 92.4%)	**13.2% more** (6.6 fewer to 41.7 more)				

*__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; **HBOT:** hyperbaric oxygen therapy; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level due to imprecision (wide confidence intervals).
[b] Downgraded one level for risk of bias as the two studies were poorly reported and appeared in a textbook of HBOT rather than a peer-reviewed journal. There was insufficient detail to provide a risk of bias assessment for any domain leading to serious concerns.
[c] Downgraded one level due to imprecision (wide confidence intervals) and one level for risk of bias as two studies were poorly reported, one of which appeared in a textbook of HBOT rather than a peer-reviewed journal. There was insufficient detail to provide a risk of bias assessment for any domain leading to serious concerns.

BACKGROUND

This review is an update of a previously published review in the *Cochrane Database of Systematic Reviews* (Issue 11, 2016) (Bennett 2016).

Description of the condition

Cancer is a significant global health problem. According to World Health Organization statistics, in 2020 more than 19 million people were diagnosed with cancer (IARC 2020). Cancer caused nearly 10 million deaths that same year (IARC 2020). Radiotherapy is a well-established treatment for suitable malignancies in a wide variety of anatomical areas. Of the approximately 1.9 million new cases of invasive cancer diagnosed annually in the USA, about 50% of people will receive radiotherapy (ACS 2023; Baskar 2012), and of these, about 40% will be long-term survivors. While radiotherapy may acutely injure any healthy tissue in the path of the radiation, this acute injury generally heals spontaneously following completion of the treatment course (Citrin 2010; Majeed 2022). 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 cancer site (Feldmeier 2012; Flannigan 2014; Stone 2003). Although any tissue may be affected, LRTI in clinical practice most commonly affects 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 progressive deterioration characterised by a reduction in the density of small blood vessels, chronic inflammation and fibrosis, until there is insufficient oxygen supplied to sustain normal tissue function (local tissue hypoxia). This situation is frequently exacerbated by secondary damage due to infection or surgery in the affected area. This progressive and delayed radiation damage may reach a critical point where the tissue breaks down to form an area of necrosis. LRTI can affect any organ system, although some tissues are more sensitive to radiation effects than others (Feldmeier 2012; Hampson 2012; Thompson 1999).

Historically, the management of these injuries has been unsatisfactory. LRTI may be life-threatening and may significantly reduce quality of life (QoL) (Citrin 2010; Majeed 2022). Conservative treatment is usually restricted to symptom management, while definitive treatment traditionally entails surgery to remove the affected tissue and extensive repair (Dalsania 2021). Surgical intervention in an irradiated field is often disfiguring and associated with an increased incidence of delayed healing, breakdown of the surgical wound or infection. Hyperbaric oxygen therapy (HBOT) has been 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 the breakdown of irradiated tissue fields. It may be defined as the therapeutic administration of 100% oxygen at environmental pressures greater than 1.5 atmospheres absolute (ATA). Administration involves placing the person in an airtight pressurised vessel designed for human occupation (PVHO), increasing the pressure within that vessel and giving 100% oxygen for respiration. This is designed to deliver a greatly increased partial pressure of oxygen to the lungs, blood and tissues. Typically, treatments involve pressurisation between 2 ATA and 2.5 ATA for periods of 60 to 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, probably mediated through stimulation of intracellular hypoxia-induced factors (HIF) via the 'hypoxia–hyperoxia paradox' whereby gross hyperoxia can induce protective and reparative changes (Camporesi 2014; Hadanny 2020; Yuan 2009). This was demonstrated by Marx and colleagues in a rabbit mandible model and further confirmed by serial tissue oxygen level measurements using electrodes placed on the overlying skin (transcutaneous oximetry ($P_{tc}O_2$)) in humans undergoing a course of therapy for radiation necrosis of the mandible (Marx 1988; Marx 1990). In the rabbit study, the mandible was irradiated and six months later, one group was 'rescued' with HBOT. The two control groups (air and 100% oxygen at 1 ATA) showed no improvement, while in the 'rescued' group (20 sessions at 2.4 ATA breathing 100% oxygen), there was an improvement in the vascularity to greater than 70% of normal. In the human study, a progressive recovery of low $P_{tc}O_2$ 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 (Camporesi 2014; Hadanny 2020). Tissue oedema is improved through the vasoconstrictive 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 (Helmers 2022; Hills 1999). In addition, improving oxygen levels will improve white cell and fibroblast function, further enhancing wound healing (Camporesi 2014). 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. In one semi-quantitative review, Feldmeier and Hampson located 71 reports involving 1193 participants across eight different tissues (Feldmeier 2002). In these people, for whom conservative treatment had failed to improve symptoms, there were clinically significant improvements in the majority. Results varied between tissue types, with neurological tissue appearing the most resistant to improvement. Only 7/71 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. Other more-focused systematic reviews investigated HBOT in radiation-induced haemorrhagic cystitis (Cardinal 2018; Villeirs 2019), cerebral radiation necrosis (Drezner 2016), irradiated dental implants (Shah 2017), radiation-induced xerostomia (Fox 2015), radiation-induced gastrointestinal complications (Yuan 2020), radiation-induced complications of the

head and neck (Ravi 2017), and radiation-induced skin necrosis (Borab 2017). Our review is an update of the 2016 Cochrane Review (Bennett 2016) of the same title and complements Feldmeier 2002 and Hoggan 2014 by using explicit Cochrane methodology to locate, quantitatively appraise and summarise the comparative data in LRTI while not discussing in any detail the non-comparative series summarised in those reviews.

HBOT is associated with the risk of adverse events including damage to the ears, sinuses and lungs from the effects of pressure; temporary worsening of short-sightedness (myopia) (Bennett 2019), claustrophobia and oxygen toxicity. The minor adverse effects of temporary myopia and middle-ear barotrauma are the most commonly encountered problems, with about 20% of people showing a greater than 1 dioptre change after 20 treatments and an incidence of barotrauma severe enough to interrupt treatment occurring in less than 2% of individuals (Bennett 2019; Jokinen-Gordon 2017). Serious adverse events are rare, for example, oxygen toxicity seizures have an incidence of one in several thousand treatments, and are unlikely to be encountered during randomised trials of the size expected to be encountered in this review. Nevertheless, HBOT cannot be regarded as an entirely benign intervention. It has further been suggested that HBOT may increase the incidence and rate of growth of tumours in people with a history of malignancy, although one comprehensive review did not support these concerns (Feldmeier 2003).

OBJECTIVES

To evaluate the benefits and harms of hyperbaric oxygen therapy (HBOT) for treating or preventing late radiation tissue injury (LRTI) compared to regimens that excluded HBOT.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs (where randomisation was intended, but the method used was clearly flawed, e.g. consecutive allocation) examining the effect on any form of LRTI of a regimen including HBOT compared to examining any treatment regimen not including HBOT.

Types of participants

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

Types of interventions

We included studies 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 with pressures between 1.5 ATA and 3.0 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 measures depend on the nature of the LRTI and the anatomical location. Some outcome measures allow pooled analysis across different anatomical locations and reflect the generally similar effect of radiation on most tissues. However, given the high clinical heterogeneity present, for this update, we have largely eliminated the overall estimates of effect across different anatomical areas.

Studies were eligible for inclusion in our quantitative analysis if they reported any of the outcomes listed under Primary outcomes and Secondary outcomes.

All anatomical areas

1. Survival from time of randomisation to death from any cause (outcome 1.1)
2. Complete or substantial resolution of clinical problem (outcome 1.2)

Specific tissues

Bone

1. Healing with complete soft tissue coverage over bone (outcome 2.1)

Head and neck soft tissues

1. Wound dehiscence (breakdown of a surgical wound) (outcome 3.1)

Urinary bladder

1. Resolution of bleeding (outcome 4.1)
2. Removal of bladder and urine diversion procedures (outcome 4.2)

Bowel

1. Resolution of bleeding (outcome 5.1)
2. Operations on the bowel such as colostomy, ileostomy or bowel resection (outcome 5.2)

Neurological tissue

1. Improvement in objective motor function (outcome 6.1)
2. Improvement in visual acuity (outcome 6.2)

Extremities

1. None additional to those listed under 'All anatomical areas' (outcome 7)

Adverse events of hyperbaric oxygen therapy

1. Recurrence of tumour (locally or remote) (outcome 8.1)
2. Visual disturbance (short- and long-term worsening of visual acuity) (outcome 8.2)
3. Damage from pressure changes (otic, sinus or pulmonary barotrauma, in the short and long term) (outcome 8.3)
4. Oxygen toxicity (short term) (outcome 8.4)
5. Withdrawal from treatment for any reason (outcome 8.5)
6. Any other recorded adverse event (outcome 8.6)

All anatomical areas

1. Resolution of pain (outcome 1.3)
2. Improvement in QoL, function or both (we will consider any measures of these outcomes, both general and organ-specific, e.g. 36-item Short Form (SF-36) or bowel bother scale) (outcome 1.4)

Specific tissues

Bone

1. Complete healing or substantial improvement (outcome 2.2)
2. Healing of tooth socket following tooth extraction in an irradiated area (outcome 2.3)
3. Resolution of sinus tract between bone and skin or mucosa (outcome 2.4)
4. Resolution of fracture or re-establishment of bony continuity (outcome 2.5)
5. Improvement in X-ray appearance (outcome 2.6)
6. QoL or functional scores (outcome 2.7)

Head and neck

1. Surgical removal of the larynx (outcome 3.2)
2. Major vessel bleeding (outcome 3.3)
3. Speed of wound healing (outcome 3.4)
4. Improvement in swelling or 'woodiness' of tissue (outcome 3.5)
5. Reversal of tracheostomy (surgical breathing hole in the trachea) (outcome 3.6)
6. QoL (outcome 3.7)

Urinary bladder

1. Complete or substantial recovery (outcome 4.3)
2. Improved cystoscopic appearance (outcome 4.4)
3. Frequency (outcome 4.5)
4. Dysuria (pain on passage of urine) (outcome 4.6)
5. Measures of functional improvement or QoL (outcome 4.7)

Bowel

1. Improvement in pain score (outcome 5.3)
2. Measures of functional improvement or QoL (outcome 5.4)

Neurological tissue

1. Improvement in sensory function (outcome 6.3)
2. Improvement in functional ability or activities of daily living (ADL) (outcome 6.4)
3. Improvement in neuropsychiatric testing (outcome 6.5)
4. Improvement in X-ray or scan appearance (outcome 6.6)
5. Reduction in steroid dose (outcome 6.7)

Extremities

1. Resolution of swelling (outcome 7.1)
2. Reduction in volume of limb (outcome 7.2)
3. Improvement in QoL and functional status (outcome 7.3)

Search methods for identification of studies

We searched the databases listed below from inception to January 2022. We further supplemented these with handsearches of the two main journals specialising in hyperbaric medicine: *Diving and Hyperbaric Medicine* (joint publication of the South Pacific Underwater Medical Society (SPUMS) and the European Undersea Medical Society (EUBS)), and *Undersea and Hyperbaric Medicine*, published by the Undersea and Hyperbaric Medical Society (UHMS).

We intended to capture both published and unpublished studies.

We initially searched in November 2004 and repeated the search in August 2008, March 2011, December 2015 and January 2022.

Electronic searches

We searched the following (from inception) in November 2004 and then repeated the searches at later dates:

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 1);
2. MEDLINE via Ovid (1966 to week 1, 2022);
3. Embase via Ovid (1980 to week 3, 2022);
4. EBSCO CINAHL (1982 to January 2022);
5. DORCTIHM (The Database of Randomised Trials in Hyperbaric Medicine (Bennett 2011), an additional database developed in our Hyperbaric facility, searched January 2022).

The search strategies for these 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 2017; Mathieu 2006; Neuman 2008; Whelan 2017), 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 studies 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

In this update, two review authors (ZCL and CPA) reviewed the results of the updated search provided by the Cochrane Information Specialist. We performed additional searches of references in articles and previously registered clinical trials. With trials that were expected to be complete but with no published literature, we attempted to contact trialists. Two review authors (ZCL and CPA) independently screened the titles and abstracts of

all studies for inclusion and consulted a third review author (MB) if required to arrive at a consensus.

In the original review, one review author (MB) was responsible for handsearching and identification of appropriate studies for consideration. For subsequent updates, including this report, three review authors 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 and retrieved the retained studies in full. The three review authors reached a consensus conclusion on these studies for inclusion or exclusion from this analysis (see Figure 1).

Figure 1. Study flow diagram.

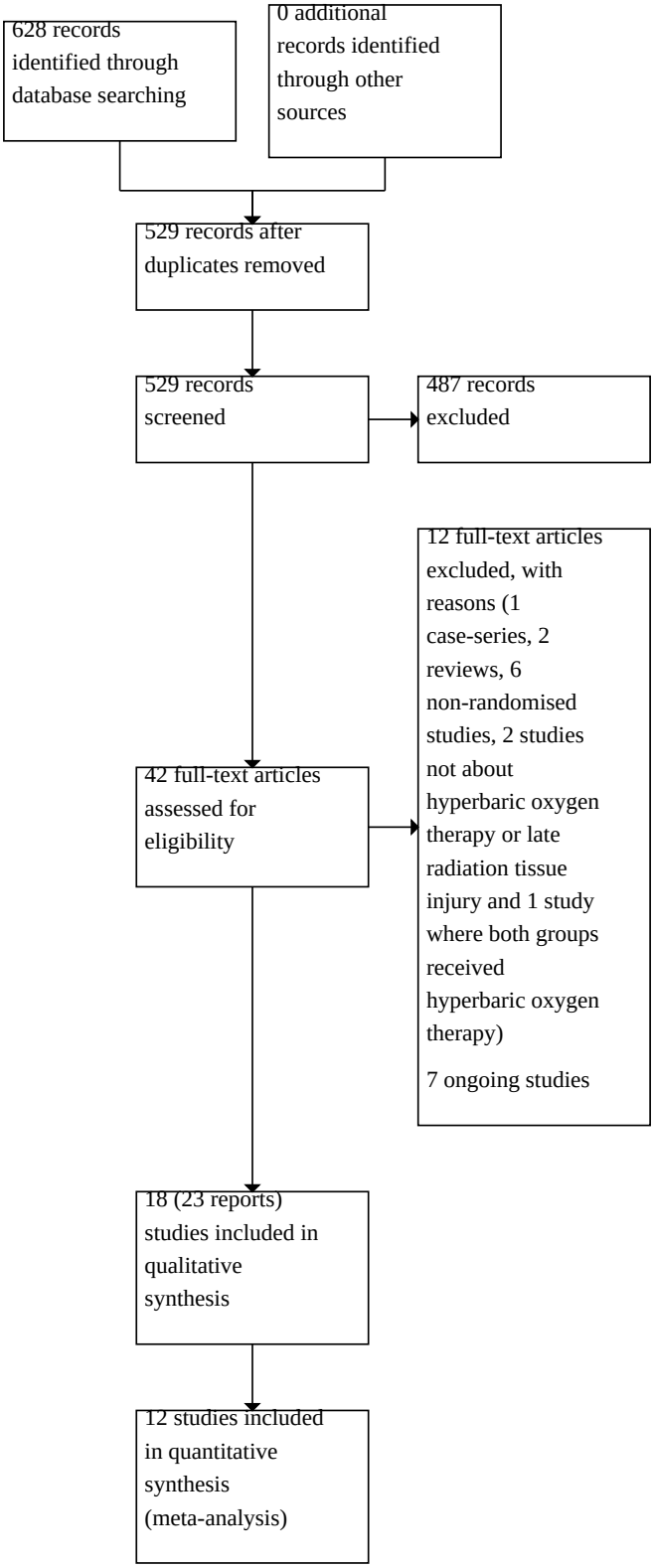
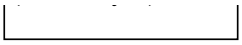


Figure 1. (Continued)



Data extraction and management

Using the data extraction form previously developed for these reviews (Appendix 6), two review authors (ZCL and CPA) independently extracted the relevant data based on the outcomes detailed in Types of outcome measures. We extracted information to inform risk of bias assessment. We contacted primary authors to request information when there were missing data or if necessary data, such as adverse events, were not clearly stated. We resolved all differences by discussion and no disputed studies required referral to a third review author.

Assessment of risk of bias in included studies

Two review authors (ZCL and CPA) independently appraised each included study to assess the risk of bias using RoB 1 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.

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 trialists?
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 study 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 study report?

Measures of treatment effect

We used CATmaker to calculate treatment effect between-group comparisons for single studies when the study authors did not do so (CEBM 2004). For all other measures of treatment effect, we used Review Manager 5 (RevMan 2020). 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 study and aggregated MDs using inverse variance weights to estimate an overall MD and its 95% confidence interval (CI). Where data were insufficient to calculate MD, we used other provided data (e.g. the difference between baseline and final results as a basis of comparison).

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

Unit of analysis issues

None of the included RCTs used cluster randomisation (e.g. by hyperbaric facility), and we did not have to reanalyse by calculating effective sample sizes (Higgins 2021). Where a study reported multiple arms, we included only the two relevant arms in a single meta-analysis. For studies presenting outcomes at multiple time points, we extracted data at all time points as subgroups.

Dealing with missing data

We attempted to contact the study authors to obtain outcome data missing from study reports and employed sensitivity analyses when this information was not forthcoming. We used the approach suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* for dichotomous outcomes using best-case and worst-case scenarios for the imputation of missing data (Higgins 2021). The best-case scenario assumed that none of the originally enroled participants missing from the primary analysis in the treatment group had a negative outcome of interest while all participants missing from the control group did. The worst-case scenario was the reverse.

For continuous outcomes, we calculated the MD based on the number of participants analysed. Where the number of participants analysed was not presented for each time point, and the trialists did not report imputed data for missing outcomes, we used the number of randomised participants in each group at baseline. Where studies reported medians and interquartile ranges instead of means and standard deviations (SD), we assumed a normal distribution, approximated the mean, and calculated the SD.

Assessment of heterogeneity

We considered clinical heterogeneity between trials when deciding whether or not to pool data and assessed statistical heterogeneity both using visual inspection of forest plots and the calculation of the I^2 statistic. If there were indications of high heterogeneity between trials, we sought to explain this using preplanned subgroup analyses (see below).

Assessment of reporting biases

There were no analyses that included sufficient studies to perform funnel plots to investigate for small-study biases. For the newly included studies in this review, we compared study protocols against published reports to assess for outcome reporting bias.

Data synthesis

We performed meta-analyses where trials identified were clinically and methodologically sufficiently similar for pooling of outcomes. We used a random-effects model when there was some evidence of between-trial heterogeneity on visual inspection or I^2 statistic, but used a fixed-effect model where both inspection and statistical heterogeneity was estimated to be low.

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. the severity of the injury.

Sensitivity analysis

We performed sensitivity analyses for missing data and risk of bias based on the presence or absence of a reliable random allocation method, concealment of allocation, and blinding of participants or outcome assessors where appropriate.

Summary of findings and assessment of the certainty of the evidence

Using our identified outcomes of interest, we summarised the primary outcomes and important secondary outcomes where data were available in Summary of findings 1. We also created a separate table for ORN and head and neck tissue-specific outcomes detailed in Summary of findings 2. These tables include a brief discussion of the importance of each major outcome, along with notes to outline any factors that importantly modify our confidence in the quantitative result. We assessed the certainty of the evidence in the summary of findings tables using the GRADE approach (Schünemann 2013).

RESULTS

Description of studies

Prior to this updated review, we had reported on the results of four search dates: December 2004, August 2008, March 2011 and December 2015. Together, these searches identified 482 publications apparently dealing with the use of HBOT for the treatment of LRTI. On the basis of screening the titles and abstracts, we excluded 454 records and retrieved the remaining 28 reports in full text. After appraisal of the full reports, we further excluded two systematic reviews with no new data (Coulthard 2002; Denton 2002), seven reports with non-random controls (Carl 2001; Craighead 2011; Gal 2003; Granstrom 1999; Maier 2000; Marson 2014; Niimi 1997), one RCT not examining HBOT (Rajaganapathy 2014), and one RCT with no quantitative data (Tobey 1979). See the Characteristics of excluded studies table.

Results of the search

Our most recent searches in January 2022 retrieved a further 146 records after the removal of duplicates. After screening the titles and abstracts, we excluded 138 records and obtained the remaining eight papers in full text. Of these reports, we included four new studies, excluded one study as it was a duplicate from a previous search and added one RCT not examining LRTI (Song 2018) to the Characteristics of excluded studies table. We added two identified study protocols to the Characteristics of ongoing studies table (Batenburg 2020; Bulsara 2019).

In total, over all searches since 2004 we identified 628 records, culled to 529 after the removal of duplicates. Of these 487 were excluded after review of title and abstract, leaving 42 records examined in full-text for eligibility. We excluded 12 records as they did not meet our inclusion criteria, filed seven records under ongoing studies, and the remaining 23 records provided the results of the 18 studies included in our quantitative review. See Figure 1.

Included studies

We included 23 reports of 18 studies (Annane 2004; Clarke 2008; Forner 2022; Glover 2016; Gothard 2010; Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b; Oscarsson 2019; Oton Sanchez 2013; Pritchard 2001; Schoen 2007; Shao 2011; Shaw 2019; Sidik 2007; Svalestad 2014; Teguh 2009).

The studies were published between 1985 and 2022 and provided data on 1071 participants, 556 (52%) receiving HBOT and 515 (48%) receiving control (see Characteristics of included studies table).

We added four new studies at this update: Forner 2022 (65 participants; 30 HBOT, 35 control); Glover 2016 (74 participants; 48 HBOT, 26 control); Oscarsson 2019 (79 participants; 41 HBOT, 38 control) and Shaw 2019 (100 participants; 47 HBOT, 53 control).

Gender

Six studies enroled more females than males (Pritchard 2001: 34 participants, all female; Gothard 2010: 58 participants, all female; Hulshof 2002: six females and one male; Clarke 2008: 106 females and 13 males; Shaw 2019: 72 females and 28 males; Glover 2016: 47 females and 37 males). Six studies enroled more males than females (Annane 2004: 59 males and nine females; Forner 2022: 55 males and 10 females; Schoen 2007: 17 males and nine females; Teguh 2009: 12 males and seven females; Svalestad 2014: 15 males and seven females; Oscarsson 2019: 57 males and 22 females). Six studies did not specify gender (Marx 1985; Marx 1999a; Marx 1999b; Oton Sanchez 2013; Shao 2011; Sidik 2007).

Radiotherapy dose

All studies required radiotherapy to have been given prior to enrolment, but the dose and any accompanying chemotherapy varied considerably between studies. Marx and colleagues required a prior exposure to a minimum of 64 Gy to the area (Marx 1999a; Marx 1999b), Teguh 2009 accepted people with 46 Gy to 70 Gy, whereas Shao 2011, Shaw 2019, and Svalestad 2014 required at least 50 Gy. None of the other studies specified a minimum dose.

Inclusions and exclusions

Annane 2004 excluded people with more advanced ORN. Clarke 2008 and Glover 2016 entered participants with radiation proctitis; Annane 2004, Forner 2022, Marx 1999a, and Marx 1999b included people with established ORN of the mandible; Hulshof 2002 enroled people with cognitive deficits following brain irradiation with at least 30 Gy; Pritchard 2001 enroled people with radiation-induced brachial plexus lesions and Gothard 2010 enroled people with arm lymphoedema, both following irradiation of the breast. Oton Sanchez 2013 enroled people with cervical fibrosis in the neck, Shao 2011 and Oscarsson 2019 enroled people with radiation cystitis, Sidik 2007 enroled people with stage I to IIIB carcinoma of the cervix and Svalestad 2014 enroled people with a clinical diagnosis of LRTI of the head and neck tissues. The other four studies treated participants without radiation tissue necrosis: Marx 1985 and Shaw 2019 enroled participants requiring tooth extraction or dental implants 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 table).

Hyperbaric oxygen therapy

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 3.0 ATA (Hulshof 2002), while all other studies utilised 2.4 or 2.5 ATA. The duration of all treatments was 80 to 90 minutes. All studies administered a total of 28 to 30 treatments, except Annane 2004, Clarke 2008, Forner 2022, Glover 2016, and Oscarsson 2019, where some people received 40 treatments and Oton Sanchez 2013 administered 25 sessions. Annane 2004 used a twice-daily treatment schedule.

Comparisons

One study compared intravesical hyaluronic acid (HA) to HBOT (Shao 2011); otherwise, there were no active comparator regimens administered to the control groups other than withholding HBOT in these studies. Four studies administered a blinded sham therapy (Annane 2004; Clarke 2008; Glover 2016; Pritchard 2001).

Follow-up

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; Oscarsson 2019; Oton Sanchez 2013; Shaw 2019; Svalestad 2014), one year (Annane 2004; Forner 2022; Glover 2016; Gothard 2010; Pritchard 2001; Schoen 2007; Teguh 2009), and 18 months (Shao 2011). Marx 1999a did not specify the time at which the outcome was measured.

Outcomes

All included studies except Oton Sanchez 2013 and Svalestad 2014 reported at least one clinical outcome of interest. Of our outcomes, these studies reported data on primary outcomes (resolution of the problem, bony continuity established, mucosal cover, wound dehiscence, and Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic (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: histological changes (Oscarsson 2019), 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 $P_{tc}O_2$, laser Doppler flowmetry (LDF), microvascular density (MVD), proliferation index (Svalestad 2014), and xerostomia (Forner 2022).

Further details are given in Characteristics of included studies table.

Excluded studies

We excluded 12 reports after review of the full-text articles (Carl 2001; Coulthard 2002; Craighead 2011; Denton 2002; Gal 2003; Granstrom 1999; Maier 2000; Marson 2014; Niimi 1997; Rajaganapathy 2014; Song 2018; Tobey 1979). Two were systematic reviews with no new data, three were non-random comparative studies, two were retrospective cohort studies and there was one report each of a case series and a case control study. The remaining three did not involve HBOT, did not involve LRTI or both groups received HBOT. See Characteristics of excluded studies table.

Studies awaiting classification

There are no studies awaiting classification.

Ongoing studies

We found seven ongoing studies of which two were published peer review study protocols (Batenburg 2020; Bulsara 2019). We contacted the authors of each, but there are no data available for inclusion. See Characteristics of ongoing studies table.

Risk of bias in included studies

The Characteristics of included studies table provides details of the quality assessment. Study quality varied widely across the included studies. Figure 2 and Figure 3 illustrate the risk of bias across the included studies.

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

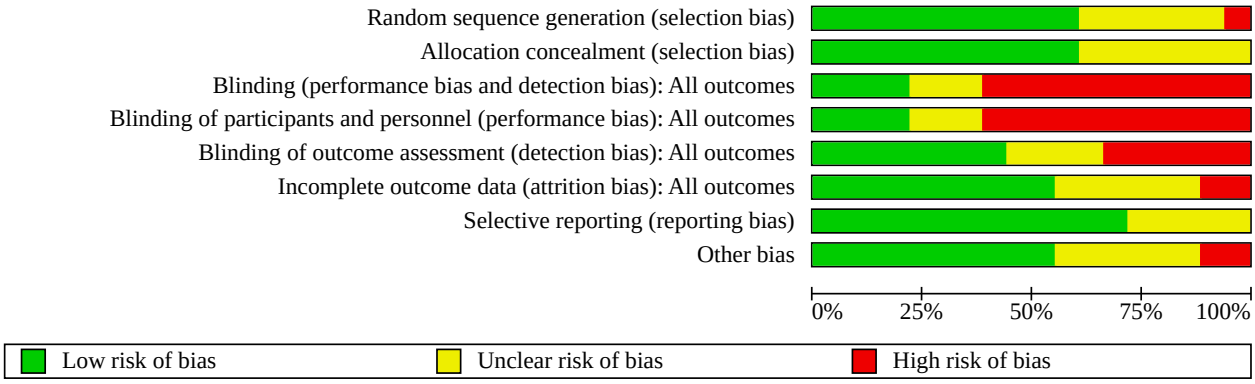


Figure 3.

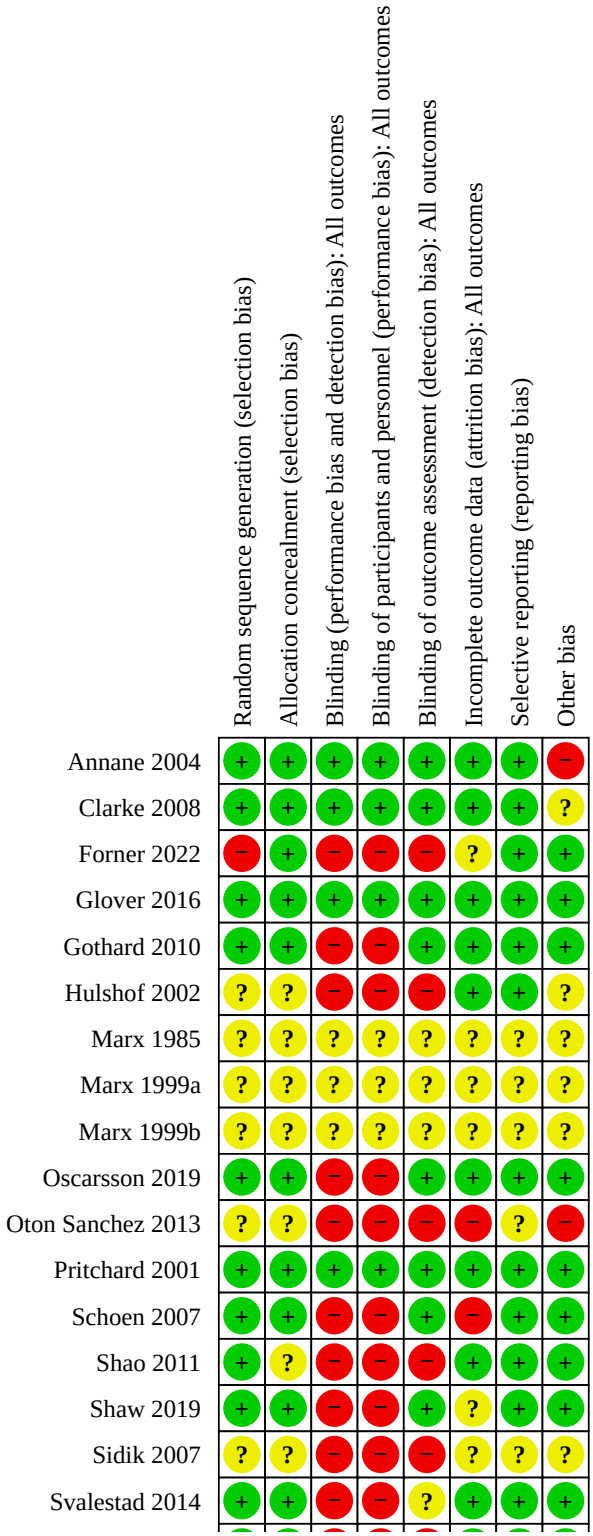
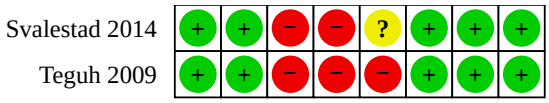


Figure 3. (Continued)



Allocation

Eleven studies described randomisation procedures, all employing a computer-generated random number table and were at low risk of bias (Annane 2004; Clarke 2008; Glover 2016; Gothard 2010; Oscarsson 2019; Pritchard 2001; Schoen 2007; Shao 2011; Shaw 2019; Svalestad 2014; Teguh 2009). Forner 2022 described randomisation without any clarification of the randomisation method and had a high risk of bias. The remaining studies did not describe randomisation procedures and were at unclear risk of bias.

Eleven studies adequately described allocation concealment and were at low risk of bias (Annane 2004; Clarke 2008; Forner 2022; Glover 2016; Gothard 2010; Oscarsson 2019; Pritchard 2001; Schoen 2007; Shaw 2019; Svalestad 2014; Teguh 2009); all except Svalestad 2014 and Shaw 2019 used a remotely located randomisation officer. There was no clear indication in any of the remaining studies that the investigators were able to predict the prospective group to which a participant would be randomly allocated.

Blinding

Four studies utilised a sham therapy in order to blind participants to HBOT and were at low risk of bias (Annane 2004; Clarke 2008; Glover 2016; Pritchard 2001), it was unclear if three studies used sham therapy (Marx 1985; Marx 1999a; Marx 1999b), while the remaining 11 studies employed no sham (high risk). Only Clarke 2008 formally tested the success of the blinding strategy.

Eight studies had a blinded outcome assessment by assessors and were at low risk of bias (Annane 2004; Clarke 2008; Glover 2016; Gothard 2010; Oscarsson 2019; Pritchard 2001; Schoen 2007; Shaw 2019). It was unclear if the assessors were blinded in four studies (Marx 1985; Marx 1999a; Marx 1999b; Svalestad 2014). The remaining six studies had no attempt at blinding outcome assessment and were at a high risk of bias (Forner 2022; Hulshof 2002; Oton Sanchez 2013; Shao 2011; Sidik 2007; Teguh 2009).

Incomplete outcome data

Seven studies reported no losses to follow-up or violation of the trial protocol and were at low risk of bias (Annane 2004; Gothard 2010; Hulshof 2002; Pritchard 2001; Shao 2011; Svalestad 2014; Teguh 2009). Clarke 2008 did not include 19 control group 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 (low risk). Oscarsson 2019 reported eight participants withdrawing consent after randomisation and five further participants discontinuing treatment for several reasons (e.g. adverse events) (low risk). Glover 2016 excluded 10 participants due to assessment forms not being returned or returned off schedule with a further nine participants excluded due to non-compliance with study interventions and gaps between assessments (low risk). Sidik 2007 reported significant losses to follow-up at six months due to death from the primary diagnosis (unclear risk). Shaw 2019 reported 23 participants withdrawing after randomisation and prior to interventions with another 19 participants lost to follow-up and withdrawing postsurgery (unclear risk). Forner 2022 excluded 32 participants due to consent problems, death, recurrence of tumours and loss to follow-up (unclear risk). Three studies provided no information (unclear risk) (Marx 1985; Marx 1999a; Marx 1999b). Oton Sanchez 2013 lost 11/37 (30%) participants randomised because of "failure to complete the study", and these were not reported (high risk). Schoen 2007 reported that six participants were lost to the final follow-up at one year (high risk).

We performed sensitivity analyses using best-case and worse-case scenarios to impute the outcome for missing data where these studies contributed data.

Glover 2016, Oscarsson 2019, and Pritchard 2001 specifically detailed an ITT analysis (two participants in the HBOT group did not complete therapy, but were included in the analysis).

Selective reporting

None of the 18 studies gave any information to suggest there were unreported outcomes. Thirteen studies were at low risk of bias. Four studies had study registration data which was used to compare the outcomes reported (Forner 2022; Glover 2016; Oscarsson 2019; Shaw 2019). Five studies were at unclear risk of bias due to the absence of reporting of trial methodology (Marx 1985; Marx 1999a; Marx 1999b; Oton Sanchez 2013; Sidik 2007).

Other potential sources of bias

Given the variation in pathology outlined in the Description of studies, there was considerable variation in participant baseline characteristics. Many studies were small and may have been subject to bias arising from unbalanced allocation to groups for unknown confounders. See Characteristics of included studies table for details of participants enroled.

Ten studies were at low risk for other biases (Forner 2022; Glover 2016; Gothard 2010; Oscarsson 2019; Pritchard 2001; Schoen 2007; Shao 2011; Shaw 2019; Svalestad 2014; Teguh 2009). Six studies had unclear risk of bias due to the cross-over nature (Clarke 2008), small number of participants (Hulshof 2002), and poor reporting (Marx 1985; Marx 1999a; Marx 1999b; Sidik 2007). Two studies were at high risk of other biases due to unusual outcome reporting (Annane 2004) and the lack of peer review (Oton Sanchez 2013).

Effects of interventions

See: **Summary of findings 1** Hyperbaric oxygen therapy (HBOT) compared to control without HBOT for late radiation tissue injury of any tissue; **Summary of findings 2** Hyperbaric oxygen therapy (HBOT) compared to control without HBOT for prevention or treatment of osteoradionecrosis of the mandible or maxilla

All anatomical areas

Primary outcomes

Survival from time of randomisation to death from any cause (outcome 1.1)

Four studies reported deaths following the intervention, of which three contributed to this analysis (Annane 2004; Schoen 2007; Sidik 2007). Three trials enroled 166 participants (76 (46%) in the HBOT group and 90 (54%) in the control group). They reported 12 deaths (16%) in the HBOT group versus 15 deaths (17%) in the control group. There was no evidence of a difference in risk of death between groups (RR 0.93, 95% CI 0.47 to 1.83; I^2 = 0%; Analysis 1.1).

One study could not contribute to this analysis. Clarke 2008 reported 5/122 (5%) deaths at one year, but this cross-over study meant that both groups had received HBOT at the time of the outcome.

Complete or substantial resolution of necrosis or tissue damage (outcome 1.2)

Seven studies reported complete resolution or significant improvement of the clinical problem, involving 501 participants (253 (50%) in the HBOT group and 248 (50%) in the control group) (Annane 2004; Clarke 2008; Forner 2022; Marx 1999a; Oscarsson 2019; Pritchard 2001; Shao 2011). Each of these individual studies enroled participants with LRTI in different anatomical locations or with grossly different disease severity, measured the outcome at different times, or compared HBOT to a different therapy. Pooled data from six studies suggested the use of HBOT may result in an increased proportion of people with substantial improvement in symptoms (RR 1.39, 95% CI 1.02 to 1.89; I^2 = 64%; Analysis 2.1). Heterogeneity was moderate as expected in examining different tissue types and including Shao 2011, which compared HBOT to intravesicular HA instillation. Pritchard 2001 did not contribute to this pooled estimate as there were no events in either arm of the study.

A sensitivity analysis was performed excluding Shao 2011 because of the different active comparator used. This analysis did not substantially reduce statistical heterogeneity (RR 1.51, 95% CI 1.07 to 2.12; I^2 = 61%; Analysis 2.2). A further sensitivity analyses for the allocation of missing data suggested our estimate of benefit was sensitive to the allocation of missing participants (best case: RR 1.7, 95% CI 1.1 to 2.6; I^2 = 82%; Analysis 2.3; worst case: RR 0.98, 95% CI 0.66 to 1.46; I^2 = 81%; Analysis 2.4).

These primary outcomes are presented in Summary of findings 1.

Secondary outcomes

Resolution of pain (outcome 1.3)

Four studies reported a change in pain score from baseline to final outcome at six to 18 months involving 272 participants (134 (49%) in the HBOT group and 138 (51%) in the control or other intervention group) (Forner 2022; Pritchard 2001; Shao 2011; Shaw 2019). Forner 2022 and Shaw 2019 compared HBOT to no HBOT without blinding, Pritchard 2001 used a sham hyperbaric exposure as a control and Shao 2011 used instillation of HA into the urinary bladder. Forner 2022, Shao 2011, and Shaw 2019 recorded pain scores using a Visual Analogue Scale (VAS), whilst Pritchard 2001 used the McGill Pain Questionnaire. Pritchard 2001 did not report SDs and could not contribute to the analysis.

Pain score (0 to 100 scale) six months after treatment

For Shao 2011, pelvic pain at six months based on a VAS was 16.0 points (SD 17.9) with HBOT versus 18.8 points (SD 14.1) with HA. The study authors did not compare the groups directly but comparison using CATmaker suggested the MD of 2.8 points in favour of HBOT was imprecise (95% CI −13.2 to 7.65).

For Pritchard 2001, pain scores increased from baseline to six months in both groups, but more so with HBOT (5.3 points with HBOT versus 1.2 points with control). The study did not report SDs around these means, precluding further analysis.

Pain score (0 to 100 scale) at 12 months after treatment

We pooled the results from Forner 2022 and Shaw 2019 comparing HBOT versus no HBOT as an adjuvant treatment for ORN involving 157 participants (74 in the HBOT group and 83 in the control group). The meta-analysis suggests that HBOT reduces pain slightly for ORN at 12 months (MD −10.72 points, 95% CI −18.97 to −2.47; I^2 = 28%; Analysis 3.1).

This result is presented in Summary of findings 2 given that the pain outcome was specific to ORN.

For Shao 2011, pelvic pain at 12 months based on a VAS was 16.0 points (SD 18.8) with HBOT versus 14.4 points (SD 13.6) with HA. The study authors did not compare the groups directly but comparison using CATmaker suggested the MD of 1.6 points in favour of HA was imprecise (95% CI −9.0 to 12.2).

For Pritchard 2001, pain scores decreased from baseline to 12 months in both groups, but more so with HBOT (5.0 points with HBOT versus 0.7 points with control). The study did not report SDs around these means, precluding further analysis.

Pain score (0 to 100 scale) at 18 months after treatment

Only Shao 2011 reported a change in pain score from baseline to 18 months. Pelvic pain based on a VAS was 13.5 points (SD 16.9) with HBOT versus 12.5 points (SD 15.3) with HA. The study authors did not compare the groups directly but a comparison using CATmaker suggested the MD of 1.0 point in favour of HA was imprecise (95% CI −9.5 to 11.5).

Improvement in quality of life, function or both (outcome 1.4)

No studies reported improvement in QoL, function or both.

Bone

Primary outcome

Healing with complete soft tissue coverage over bone (outcome 2.1)

Two studies reported the achievement of complete mucosal cover in participants with ORN, involving 172 participants (83 (48%) in the HBOT group and 89 (52%) in the control group) (Annane 2004; Marx 1999a). The clinical situation was very different in the people included in these two studies and pooled analysis confirmed there was a high degree of statistical heterogeneity, so the results are given for individual studies here.

Marx 1999a included 104 participants with advanced ORN requiring complex surgery (all including hemi-mandibulectomy) for definitive treatment. A total of 48/52 (92%) participants in the HBOT group achieved mucosal covering versus 34/52 (65%) participants in the standard care group; this difference was considered clinically

important (RR of achieving mucosal cover with HBOT 1.4, 95% CI 1.1 to 1.8).

Annane 2004 enroled 68 participants with relatively minor grades of ORN and compared HBOT versus standard oral care. A total of 18/31 (58%) participants in the HBOT group achieved mucosal cover versus 22/37 (60%) in the standard care group. This trial was terminated early after an interim analysis suggested futility in proving the clinical hypothesis (RR for achieving mucosal cover 1.0, 95% CI 0.7 to 1.6).

Secondary outcomes

Complete healing or substantial improvement of bone necrosis (outcome 2.2)

Three studies reported on bone necrosis, all involving the mandible (Annane 2004; Forner 2022; Marx 1999a). These studies reported on 239 participants (113 (47%) in the HBOT group and 126 (53%) in the control group). A total of 75/113 (66%) participants in the HBOT group were resolved or substantially improved versus 64/126 (51%) participants in the control group at one year. HBOT may result in little to no difference in the improvement of ORN (RR of healing with HBOT 1.26, 95% CI 0.87 to 1.82; I^2 = 57%; Analysis 4.1).

Given the high heterogeneity, we performed a subgroup analysis based upon severity of injury (Annane 2004 excluded all severe cases from enrolment). This subgroup analysis eliminated statistical heterogeneity and two remaining studies suggested those who received HBOT were more likely to resolve or substantially improve (RR 1.44, 95% CI 1.19 to 1.75; I^2 = 0%). See Summary of findings 2.

Healing of tooth socket following tooth extraction or implant in an irradiated area (outcome 2.3)

Three studies reported on this outcome but each enroled clinically different groups of participants and we were unable to pool the results (Marx 1985; Schoen 2007; Shaw 2019).

Marx 1985 reported on the prevention of ORN when removing teeth in a previously irradiated area. This study enroled 74 people requiring tooth extraction in a field irradiated with at least 6000 cGy administered more than six months prior to enrolment and compared HBOT (2.4 ATA for 90 minutes daily for 20 sessions pre-extraction and 10 sessions postextraction) to the administration of penicillin (500 mg six hourly for 10 days). The authors reported HBOT was effective in reducing the proportion of participants who developed ORN in at least one socket from 30% in the control group to 5% in the HBOT group (absolute risk reduction 25%, 95% CI 8% to 41%; number needed to treat for an additional beneficial outcome (NNTB) to achieve one extra person free from ORN 4, 95% CI 2 to 13).

Shaw 2019 enroled 100 people having either tooth extraction (84% of participants) or dental implants (16%) but did not report the groups separately and did not supply the details on request. These study authors reported no important difference in the rate of development of ORN between participants who received amoxycillin orally and chlorhexidine mouthwashes compared to the same regimen plus HBOT (2.4 ATA for 90 minutes daily for 20 sessions pre-extraction and 10 sessions postextraction). A total of 3/47 (6%) participants in the HBOT group developed ORN versus 4/53 (7.5%) in the control group.

Schoen 2007 enroled 26 people having (exclusively) dental implants (13 in each group). The study authors reported only one participant who developed ORN in the HBOT group (RR with HBOT 1.1, 95% CI 0.8 to 1.5).

Resolution of a sinus tract between bone and skin or mucosa (outcome 2.4)

No studies reported resolution of a sinus tract between bone and skin or mucosa.

Resolution of fracture or re-establishment of bony continuity (outcome 2.5)

One study reported the establishment of bony continuity, involving 104 participants (52 in the HBOT group and 52 in the control group) (Marx 1999a). Forty-eight (92%) participants in the HBOT group achieved continuity versus 34 (65%) in the control group, which study authors stated as clinically important. The NNTB to achieve one further case with bony continuity with the application of HBOT was 4 (95% CI 2 to 8).

Improvement of radiographic changes (outcome 2.6)

No studies reported improvement of radiographic changes.

Quality of life or functional scores (outcome 2.7)

Schoen 2007 enroled 26 participants (13 in the HBOT plus antimicrobial therapy group and 13 in the antimicrobial therapy alone group). This study reported on several measures of function and QoL relating to ORN. None suggested an important difference between groups, with control participants generally scoring slightly better.

The study assessed the physical, psychological and social impact using the Oral Health Impact Profile (0 best to 36 worst) at one year (mean score 15.0 (SD 7.3) in the HBOT group versus 12.7 (SD 9.7) in the control group) and the Groningen Activity Restriction Scale – Dentistry (0 best to 22 worst) at one year (mean 5.3 (SD 5.5) in the HBOT group versus 4.3 (SD 7.4) in the control group). There was no evidence of differences between groups.

Global QoL estimates using the 30 question 'core questionnaire' of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module (EORTC QLQ-H&N35) (0 to 100 scale, higher scores indicate better QoL) at 12 months were 66.7 (SD 13.6) in the HBOT group versus 84.3 (SD 19.7) in the control group.

Shaw 2019 randomised 144 participants but reported on only 47 participants in the HBOT group and 53 participants in the control group. This study used the University of Washington Quality of Life Questionnaire to investigate the effect of HBOT. The overall score was a combination of several domains, but the study authors reported only the Physical score and the Social score. The Physical subscale score was computed as a mean of six domain scores: chewing, swallowing, speech, taste, saliva and appearance (score 0 worst to 100 best) and a change of 12 units was deemed 'large'. There was little change at 12 months with both groups scoring about 68 (obtained from graph). The composite Social score was compiled similarly from six subscale scores and at 12 months the mean score in the HBOT group was approximately 81 and that in the control group was 70. Neither had changed substantially from baseline (obtained from graph).

Head and neck soft tissues

Primary outcomes

Wound dehiscence (outcome 3.1)

Two studies reported comparative data for wound dehiscence postsurgery with HBOT treatment, involving 264 participants (Marx 1999a; Marx 1999b). There were 8/132 (6.1%) instances of wound dehiscence in the HBOT group compared to 37/132 (28%) in the control group. HBOT may result in a reduction in the risk of wound dehiscence following operative treatment for ORN (RR 0.24, 95% CI 0.06 to 0.94; I^2 = 70%, NNTB 5; Analysis 5.1). Analysis for heterogeneity suggested a high proportion of variability between studies was not due to sampling variability, and so this comparison was made using a random-effects model. See Summary of findings 2.

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 hemi-mandibulectomy 2.2, 95% CI 0.8 to 5.9; Marx 1999a; RR following soft tissue flap or graft 8.7, 95% CI 2.7 to 27.5; 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).

Secondary outcomes

Surgical removal of the larynx (outcome 3.2)

No studies reported removal of the larynx.

Major vessel bleeding (outcome 3.3)

No studies reported major vessel bleeding.

Speed of wound healing (outcome 3.4)

No studies reported speed of wound healing.

Improvement in swelling or 'woodiness' of tissue (outcome 3.5)

Oton Sanchez 2013 reported the proportion of people with an improvement of at least one grade in the severity of cervical fibrosis using the appropriate LENT-SOMA Scale. This study was reported in abstract form. These study authors randomised 37 people and reported the results on 26 participants (13 in each group). They compared the use of pentoxifylline plus tocopherol (drug only) versus pentoxifylline plus tocopherol plus a course of 25 sessions of HBOT (drugs plus HBOT). At six months, 10/13 (77%) participants in the group receiving HBOT reported improvement versus 4/13 (31%) participants in the drug-only group. The study authors judged this to be clinically important. The NNTB was estimated at 3 (95% CI 2 to 14).

Reversal of tracheostomy (outcome 3.6)

No studies reported reversal of tracheostomy.

Quality of life (outcome 3.7)

Teguh 2009 enroled 19 participants (8 (42%) in the HBOT group and 11 (58%) in the no treatment control group). HBOT was commenced very early, only two days after completion of radiotherapy. The study reported QoL in the form of items relating to xerostomia and dysphagia using the EORTC QLQ-H&N35 at several time points. They also determined a VAS for dry mouth and pain in the mouth. We reported the results at 12 months, but the study authors used (quote) "regression analysis based on maximum likelihood estimation and incorporating the longitudinal character of the data."

The scores were generally better in the HBOT arm (P values from study author). At 12 months, the EORTC QLQ-H&N35 sticky saliva score (0 = nil, 100 = maximum) was 25 in the HBOT group versus 62 in the control group (P = 0.01), EORTC QLQ-H&N35 scores for dry mouth (0 = nil, 100 = maximum) were 28 for in the HBOT group versus 92 in the control group (P = 0.009), EORTC QLQ-H&N35 scores for difficulty swallowing (0 = nil, 100 = maximum) were 7 in the HBOT group versus 40 in the control group (P = 0.011); VAS for 'dry mouth' (0 = nil, 10 = maximum) were 3.4 in the HBOT group versus 7.2 in the control group (P value not given) and VAS for pain in the mouth (0 = nil, 100 = maximum) were 0.8 in the HBOT group versus 6.6 in the control group (P < 0.0001).

Urinary bladder

Primary outcomes

Resolution of bleeding (outcome 4.1)

One study compared the effects of two alternative therapies rather than HBOT versus no treatment or sham for resolution of bleeding (Shao 2011). The study included 36 participants (20 (56%) in the HBOT group and 16 (44%) in the intravesicular HA group). Ten (50%) participants in the HBOT group had complete resolution at one year versus 12 (75%) in the HA group. At 18 months, nine (45%) participants remained resolved in the HBOT group versus eight (50%) in the HA group. Analysis using Fisher's Exact Test found no evidence of a difference between groups and risk analysis suggested the RR of resolution with HBOT was 0.7 (95% CI 0.4 to 1.1) at 12 months and 0.9 (95% CI 0.5 to 1.8) at 18 months.

Removal of bladder or urinary diversion procedures (outcome 4.2)

No studies reported removal of bladder or urinary diversion procedures.

Secondary outcomes

Complete or substantial recovery (outcome 4.3)

Two studies reported complete or substantial recovery (Oscarsson 2019; Shao 2011). The studies enroled a total of 109 participants (59 (54%) in the HBOT group and 50 (46%) in the control or HA instillation group). We could not pool results due to the clinical heterogeneity introduced by comparison with the alternative treatment of HA in Shao 2011.

Oscarsson 2019 reported improved outcomes with 25/39 (64%) participants in the HBOT group versus 6/34 (18%) participants in the control group (RR 3.63, 95% CI 1.69 to 7.79). Shao 2011 found no difference in the chance of improvement between groups with 15/20 participants improving in the HBOT group versus 12/16 participants in the HA group (RR 1.00, 95% CI 0.68 to 1.46) (Analysis 6.1).

Improved cystoscopic appearance (outcome 4.4)

No studies reported improved cystoscopic appearance.

Frequency (outcome 4.5)

Shao 2011 reported the daily urinary frequency in 20 participants in the HBOT group and 16 in the HA instillation group at both 12 and 18 months. At 12 months, the HBOT group reported a daily frequency

of 9.7 (SD 1.98) episodes while in the HA group there were 8.9 (SD 1.4) episodes. The difference was 0.8 episodes fewer with HA (95% CI −1.3 to 2.9). Similarly, at 18 months the HBOT group mean was 10.0 (SD 2.0) episodes and the HA mean was 10.3 (SD 1.5) episodes (MD 0.3, 95% CI −1.9 to 2.5).

Dysuria (outcome 4.6)

No studies reported dysuria.

Measures of functional improvement or quality of life (outcome 4.7)

One study reported overall QoL. Oscarsson 2019 enroled 87 participants with a diagnosis of radiation cystitis (42 (48%) received 30 to 40 HBOT sessions and 45 (52%) received standard care (control)). At six months' follow-up, the study authors used the SF-36 to assess overall QoL on 40 people in the HBOT group and 35 in the standard care alone. The mean SF-36 General Health score was 62.1 (SD 21.0) in the HBOT group and 50.9 (SD 22.7) in the standard care group (MD 11.2, 95% CI 1.3 to 21.2). The mean SF-36 Physical Functioning score was 76.7 (SD 22.6) in the HBOT group and 66.3 (SD 26.0) in the standard care group (MD 10.4, 95% CI −0.7 to 21.5).

Two studies reported pain severity after treatment. Shao 2011 found little difference between 16 participants receiving HBOT and 20 participants receiving HA instillation (VAS 1 to 10: mean 1.6 (SD 1.9) in the HBOT group and 1.4 (SD 1.4) in the HA group). The MD was 0.2 in favour of HA (95% CI −1.7 to 2.1). Oscarsson 2019 used a 100-point scale where a lower score indicated worse symptoms. They found lower scores in the standard care group at six to eight months (mean 73.4 (SD 24.9) in the HBOT group and 58.9 (SD 29.3) in the standard care group; MD −14.5, 95% CI −26.8 to −2.2).

For functional assessment, Oscarsson 2019 reported a primary outcome of the overall difference between groups for the Expanded Prostate Cancer Index Composite (EPIC) score, which calculates an index of functionality and bother (low scores indicate worse conditions). At six to eight months, the HBOT group had a mean EPIC urinary score of 65.5 (SD 24.6) while the score in the standard therapy group was 48.8 (SD 24.2). The MD between groups was 16.7 (95% CI 5.6 to 27.8).

Oscarsson 2019 reported a surgeon-assessed severity score, the Late Radiation Morbidity Grading Scheme (LRMGS) for the urinary bladder to assess epithelial atrophy, telangiectasia, haematuria, bladder capacity and presence of necrosis or ulcerations (Grade 0 indicates normal findings at cystoscopy, whereas pathology is graded from 1 to 4). The final grade was determined by a blinded and independent examiner. At six to eight months, 25/39 participants in the HBOT group had improved versus 6/34 (18%) in the standard treatment group (P = 0.001). We calculated an NNTB of 3 (95% CI 2 to 5).

Bowel

Primary outcomes

Resolution of bleeding (outcome 5.1)

Only one study reported the proportion of participants with resolution or significant improvement immediately after completion of therapy in isolation (Clarke 2008). The study enroled 119 participants (64 in the HBOT group and 56 in the control group). Twenty-nine (46%) participants in the HBOT group achieved complete resolution or significant improvement versus 15 (27%) in the control group (RR 1.7, 95% CI 1.0 to 2.9). This result was sensitive to the allocation of missing data based on the per-protocol analysis (best-case: RR 2.7, 95% CI 1.7 to 4.5; worst case: RR 0.7, 95% CI 0.5 to 0.9). The absolute difference was 19% in favour of HBOT (NNTB 5).

Operations on the bowel (outcome 5.2)

No studies reported operations on the bowel.

Secondary outcomes

Improvements in pain score (outcome 5.3)

No studies reported improvements in pain scores.

Measures of functional improvement or quality of life (outcomes 5.4)

LENT-SOMA scores

Three studies reported changes in LENT-SOMA scores for bowel symptoms (Clarke 2008; Glover 2016; Sidik 2007). The studies measured the outcome at different time points and reported outcomes in different ways making the pooling of data impossible.

Clarke 2008 enroled 150 participants (75 in each group). At three months, the mean improvement in LENT-SOMA score was greater in the HBOT group (5.0 in the HBOT group versus 2.6 in the control group; P = 0.002). All participants in the control group crossed over to receive HBOT at this time, making further comparisons unhelpful.

Glover 2016 enroled 84 people with late radiation proctitis (55 (66%) in the HBOT group and 29 (33%) in the sham exposure group). At 12 months, the study authors reported the median rectal scores and reported no important differences between groups (5 (IQR 3 to 8) in the HBOT group versus 4.5 (IQR 2 to 8) in the sham exposure group; P = 0.11). The study also reported the intestinal LENT-SOMA scores at 12 months and reported no differences between groups (2.5 (IQR 1 to 4) in the HBOT group versus 1 (IQR 1 to 4) in the sham exposure group; P = 0.16).

Sidik 2007 enroled 65 participants (32 in the HBOT group and 33 in the control group). The study authors reported the percentage change in LENT-SOMA scores at six months (improved scores by 33.6% (SD 57.6%) in the HBOT group versus worsened by 19.7% (SD 69.4%) in the control group; P = 0.008).

Quality of life scores

Glover 2016 reported bowel function using the Inflammatory Bowel Disease Questionnaire (IBDQ) including 69 participants (46 (67%) in the HBOT group and 23 (33%) in the control group). Higher scores indicate better outcomes (range 10 to 70). At 12 months, there was no difference between groups (median IBDQ score: 51 (IQR 36 to 62) in the HBOT group versus 53 (IQR 40 to 59) in the control group; P = 0.5). Similarly, this study reported the subset of IBDQ scores for rectal bleeding in 40 participants (29 (73%) in the HBOT group and 11 (27%) in the control group). There was little difference between median scores (6 (IQR 3 to 7) in the HBOT group versus 4 (IQR 2 to 6) in the control group; P = 0.09).

Clarke 2008 reported the Bowel Bother subscale of the EPIC Composite Bowel Domain QoL scale at the completion of therapy. There was a mean improvement of 14.1% in the HBOT group (P = 0.0007) compared with a mean improvement of 5.8% in the sham group (P = 0.15).

Sidik 2007 reported the percentage improvements in the Karnofsky QoL scale at six months (range 0% (dead) to 100% (normal)). There was a mean improvement of 15.3% (SD 14.7%) in the HBOT group compared to 2.5% (16.1%) in the control group (P = 0.007).

Neurological tissue

Primary outcomes

Improvement in objective motor function (outcome 6.1)

No studies reported improvement in objective motor function.

Improvement in visual acuity (outcome 6.2)

No studies reported improvement in visual acuity.

Secondary outcomes

Improvement in sensory function (outcome 6.3)

Warm sensory threshold

One study reported warm sensory threshold at one week and one year after completion of treatment (Pritchard 2001). The study enroled 34 participants (17 in each group). The mean threshold temperature for reporting a warm sensation (lower figure indicates an improvement in function) at one week after therapy (compared to pretreatment baseline) was reduced in the HBOT group, but not in the control group (−0.1 °C in the HBOT group versus 1 °C in the control group; MD 1.1 °C, 95% CI −2.0 to 4.1; P = 0.47). At one year after therapy, the mean threshold for reporting a warm sensation was increased in both groups (0.5 °C in the HBOT group versus 1.4 °C in the control group; MD −0.9 °C, 95% CI −4.0 to 2.2; P = 0.58).

Improvement in functional ability or activities of daily living (outcome 6.4)

In Pritchard 2001, the mean score for self-rated general health was similar in both groups at 12 months (58.8 in the HBOT group versus 61.1 in the control group). Using the standard errors given to calculate SDs, analysis gave a P value of 0.79. The mean score for self-rating of physical functioning was similar in both groups at 12 months (53.5 in the HBOT group versus 57.5 in the control group). Using the standard errors given to calculate SDs, analyses gave a P value of 0.61.

Improvement in neuropsychological testing (outcome 6.5)

One study reported the results of neuropsychological tests at three months, involving seven participants (four in the HBOT group and three in the control group) (Hulshof 2002). The study authors concluded there was little evidence of a treatment effect with HBOT; however, they combined the results of each group before and after testing, so a randomised comparison was not possible.

Improvement in X-ray or scan appearance (outcome 6.6)

No studies reported improvements in X-ray or scan appearance.

Reduction in steroid dose (outcome 6.7)

No studies reported reduction in steroid dose.

Extremities

Secondary outcomes

Resolution of swelling (outcome 7.1)

One study reported resolution of lymphoedema at six months in the ipsilateral arm following irradiation for breast cancer, involving 34 participants (17 in each group) (Pritchard 2001). Two (12%) participants in the HBOT group achieved resolution, while none in the control group did so (P = 0.29).

Reduction in volume of limb (outcome 7.2)

One study reported a relative reduction in arm volume at 12 months following breast irradiation, involving 46 participants (58 enroled but 12 missing at 12 months) (30 in the HBOT group and 16 in the control group) (Gothard 2010). There was no 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) (reduction: MD 2.6%; P = 0.86). The study authors also reported the proportion of participants achieving a greater than 8% reduction in the volume of the arm (9/30 (30%) in the HBOT group versus 3/16 (19%) in the control group; P = 0.5).

Improvement in quality of life and functional status (outcome 7.3)

One study reported lymphoedema-related function at 12 months, involving 58 participants with lymphoedema following irradiation for breast cancer (38 in the HBOT group and 20 in the control group) (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 difference between the groups at 12 months (median score: 37.5 (IQR 20.8 to 52.1) in the HBOT group versus 45.8 (IQR 13.0 to 62.5) in the control group; P not reported).

Gothard 2010 also reported no differences in QoL between groups at 12 months, but provided no data.

Adverse events

Primary outcome

Recurrence of tumour (outcome 8.1)

No studies reported recurrence of tumour.

Visual disturbances (outcome 8.2)

Five studies with 438 participants reported comparative data on visual changes (Clarke 2008; Glover 2016; Gothard 2010; Oscarsson 2019; Shaw 2019). Pooling suggested visual changes in 29/243 (12%) participants in the HBOT group versus 3/195 (1.5%) participants in the control group. HBOT results in a reduction in visual acuity at the end of treatment (RR 4.03, 95% CI 1.65 to 9.84; I^2 = 0%; number needed to treat for an additional harmful outcome (NNTH) 10; Analysis 7.1).

Damage from pressure changes (outcome 8.3)

Six studies with 506 participants reported comparative data on otic barotrauma (Annane 2004; Clarke 2008; Glover 2016; Gothard 2010; Oscarsson 2019; Shaw 2019). There was important clinical heterogeneity between studies with Annane 2004 and Glover 2016 both using an active sham pressurisation comparator that involved compression while the remaining four studies did not use compression in control participants. This analysis suggests that there was little difference between groups when both groups were

compressed (RR 1.07, 95% CI 0.52 to 2.21; I^2 = 74%); however, there was an important increase in the risk of ear barotrauma with active HBOT if the control participants were not compressed (RR 9.08, 95% CI 2.21 to 37.26; I^2 = 0%). A total of 35/274 (13%) participants undergoing HBOT reported ear barotrauma suggesting an NNTH of eight participants (Analysis 7.2).

See Summary of findings 1.

Oxygen toxicity (short-term) (outcome 8.4)

No studies reported oxygen toxicity.

Withdrawal from treatment for any reason (outcome 8.5)

No studies reported withdrawal from treatment for any reason.

Any other recorded adverse event (outcome 8.6)

No studies reported any other recorded adverse event.

Summary of studies not reported

Svalestad 2014 enroled 22 participants with clinical LRTI affecting the oral mucosa that were referred for consideration of HBOT. Fourteen (64%) participants were allocated to HBOT and eight (36%) participants to delayed treatment for a minimum of six months. The first publication reported on LDF and $P_{tc}O_2$ results before and after treatment in all participants. The later publication added histopathological data on the 20 participants who consented to tissue biopsies of the irradiated gingival mucosa. It reported all outcomes as changes from baseline in each group rather than a direct comparison between groups.

The study reported an increase in LDF (measured as blood flow expressed in 'perfusion units') in the HBOT group at six months after treatment, but not in the controls (HBOT: baseline cheek blood flow 104 (SD 64) and at six months 306 (SD 237); P < 0.05; control: baseline cheek blood flow 142 (SD 67) and at six months 143 (SD 79); P > 0.05). Similarly, there was an increase in $P_{tc}O_2$ during the course of the study in the HBOT group, but not in the control group (HBOT: baseline 14.0 mmHg (SD 5.8) and six months 19.8 mmHg (SD 6.5); P < 0.05; control: 14.0 mmHg (SD 5.0) and 12.7 mmHg (SD 4.6); P > 0.05).

In the second publication, both MVD and area were increased in the subepithelial tissue following HBOT, but not in the control group (HBOT: baseline 1.5 (SD 0.6) vessels/mm^2 and at six months 4.4 (SD 1.9) vessels/mm^2; P = 0.003; control: baseline 1.5 (SD 0.6) vessels/mm^2 and at six months 1.6 (SD 0.5) vessels/mm^2; P > 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

We updated this review following a search in January 2022; it includes four new studies enroling people with ORN or to prevent the development of ORN (Forner 2022; Shaw 2019), radiation cystitis (Oscarsson 2019), and radiation proctitis (Glover 2016). Overall, we included data from 18 studies including 1071 people.

HBOT may not prevent death at one year (RR 0.93, 95% CI 0.47 to 1.83; I^2 = 0%; 3 studies, 166 participants; low-certainty evidence due to imprecision in our estimate and a high risk of bias). There is some evidence that HBOT may result in complete resolution or provide significant improvement of LRTI (RR 1.39, 95% CI 1.02 to 1.89; I^2 = 64%; 6 studies, 468 participants; low-certainty evidence due to high attrition rate and a high risk of bias) and HBOT may result in a reduction in wound dehiscence following head and neck soft tissue surgery (RR 0.24, 95% CI 0.06 to 0.94; I^2 = 70%; 2 studies, 264 participants; low-certainty evidence due to imprecision in our estimate and high risk of bias). In addition, HBOT reduces pain slightly for ORN at 12 months (MD −10.72, 95% CI −18.97 to −2.47; I^2 = 40%; 2 studies, 162 participants; moderate-certainty evidence due to imprecision in our estimate).

Regarding adverse events, HBOT results in a reduction in visual acuity (RR 4.03, 95% CI 1.65 to 9.84; 5 studies, 438 participants; high-certainty evidence). There was a risk of otic barotrauma in those receiving HBOT when no sham pressurisation was used for the control group (RR 9.08, 95% CI 2.21 to 37.26; I^2 = 0%; 4 studies, 357 participants; high-certainty evidence), but no such increase when a sham treatment was employed (RR 1.07, 95% CI 0.52 to 2.21; I^2 = 74%; 2 studies, 158 participants; high-certainty evidence).

Overall completeness and applicability of evidence

This updated review identified 18 studies investigating the use of HBOT for tissue with LRTI, and we believe these represent all randomised studies in humans in this area, both published and unpublished, at the time of searching the listed databases.

These studies were published over a 37-year period up to 2022, and from a large geographical area. The studies enroled a wide variety of participants with LRTI, and HBOT seems to have been generally well-tolerated and safe. Clinical heterogeneity, differences in the outcomes measured, and trial reporting resulted in the ability to only pool few analyses with these data and consequently our conclusions remain limited.

LRTI may affect any irradiated tissue, and in this respect the data presented here from RCTs are incomplete, with some sites (e.g. brain or peripheral nerves) very poorly represented. The use of HBOT should only be evaluated with this in mind.

Furthermore, 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 severity of the injury. However, the paucity of eligible studies and poor reporting of some studies suggested these analyses would not be informative for the most part. Of note, a subgroup analysis of the use of HBOT to prevent ORN based on a presumption of LRTI severity (diseased teeth for removal versus healthy bone into which implants are planned) suggested there was little benefit with HBOT when tissue was healthier and the risk of ORN was low (Schoen 2007; Shaw 2019) compared to an apparent benefit when there was active tooth disease and the rate of ORN higher (Marx 1985).

HBOT appears to be a safe option for treatment of people with LRTI. This updated review found six studies reporting the incidence of adverse events. While there are a number of minor complications that may occur commonly, HBOT is a safe treatment option with no major complications reported in these studies.

Visual disturbance, usually reduction in visual acuity secondary to conformational changes in the lens, is very commonly reported — perhaps as many as 68% of people having a course of 30 treatments (Bennett 2019). While the great majority of people recover spontaneously over a period of days to weeks, a small proportion of people continue to require visual correction to restore sight to pretreatment levels. Middle-ear barotrauma is also common on compression and generally mild, easily treated or recovers spontaneously with ear equalisation. Neither of these common events requires abandonment of therapy.

We believe the results reported here can be widely applied to people with a diagnosis of LRTI of the head, neck and pelvis, where some meaningful data exist; however, we remain unable to present data that would support or refute the use of HBOT in other tissues.

Quality of the evidence

Many of the studies enroled modest numbers of participants and a number of studies were poorly reported. Our confidence in outcomes related to ORN was downgraded due to poor reporting of potential biases in two studies and imprecision in the estimated improvements with HBOT (Summary of findings 2). Other problems encountered in this review were the poor methodological quality of some of these studies (particularly Marx 1999a; Marx 1999b), variability in entry criteria, nature and timing of outcomes, with poor reporting of both outcomes and methodology. In particular, there is a possibility of bias due to the extent of tissue damage on entry to these studies, as well as from non-blinded management decisions in three studies (Marx 1985; Marx 1999a; Marx 1999b). Further, it is unclear when the participants for Marx 1999a and Marx 1999b were recruited as these studies may represent work from some years earlier.

However, the four new studies added in this update have generally more robust methodology, are better reported and have generated an improved quality of the evidence.

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 studies more likely to achieve reporting. There were insufficient included studies to allow formal investigation of such a bias. With regard to long-term outcomes following HBOT and any effect on the QoL for these people, we located few relevant data. Encouragingly, we have identified seven ongoing studies that seem likely eligible for inclusion in future updates of this review (Batenburg 2020; Bulsara 2019; NCT03144206; NCT00087815; NCT03916068; NCT02714465; NCT04934644).

Agreements and disagreements with other studies or reviews

Our review is broadly consistent with other 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 people suffering from radiation proctitis and non-neurological STRI (soft tissue radiation-related injuries) of the head and neck." They called for further high-quality studies 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.

We included only one study involving haemorrhagic cystitis in this review but it was in agreement with other broader systematic reviews including non-RCTs (Cardinal 2018; Villeirs 2019). Two studies included in this review involving dental implants have suggested no clear benefit with HBOT, a finding in disagreement with the review of Shah 2017, which included non-randomised studies. Our review is in broad agreement regarding the treatment of radiation proctitis, based on the single included study, with the findings of a systematic review with wider study inclusion criteria (Yuan 2020).

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 study did not test the usual treatment regimen employed for the management of ORN (the combination of HBOT and surgical excision of necrotic bone) and may not, therefore, be directly comparable with the other studies 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). In contrast, 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. Second, 66/134 (49%) participants presenting with ORN during the study period were ineligible for inclusion, making a generalisation of the findings of this study to more advanced cases of ORN (such as those presented in Marx 1999a and Marx 1999b) problematic. Finally, this study was stopped (according to predefined 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 study.

AUTHORS' CONCLUSIONS

Implications for practice

There is low- to moderate-certainty evidence that hyperbaric oxygen therapy (HBOT) improves outcomes in late radiation tissue injury (LRTI) affecting bone and soft tissues of the head and neck and some evidence for improvement in radiation cystitis and proctitis. However, new evidence suggests HBOT may not improve outcomes in osteoradionecrosis or prevent death. There is no evidence of any important clinical effect on neurological tissues, either peripheral or central. Our conclusion remains that the application of HBOT for selected individuals and tissues is justified.

While the small number of studies, modest numbers of participants, and methodological and reporting inadequacies of some of the primary studies included in this review demand a cautious interpretation, the pathology of radiation injury suggests many tissues may 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

Given the new conflicting study results, there is a strong case for further large randomised studies 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 studies 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. total number of treatment sessions;
5. appropriate supportive therapy to which HBOT would be an adjunct;
6. use of an effective sham therapy;
7. effective and explicit blinding of outcome assessors;
8. appropriate outcome measures including all those listed in this review;
9. careful elucidation of any adverse events;
10. the cost-utility of the therapy.

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We would like to dedicate this review to Prof Michael Bennett who has worked extensively on this current update and mentored the lead author. He sadly passed away prior to the publishing of this review update.

REFERENCES

References to studies included in this review

Annane 2004 *{published data only (unpublished sought but not used)}*10.1200/JCO.2004.09.006

Annane D, Depondt J, Aubert P, Villart M, Gehanno P, Gajdos P, et al. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 Study Group. *Journal of Clinical Oncology* 2004;**22**(24):4893-900.

Clarke 2008 *{published data only (unpublished sought but not used)}*10.1016/j.ijrobp.2007.12.048

Clarke D, Tenorio C, Dominguez L, Toklu A, Hussey J. Treatment of radiation necrosis with hyperbaric oxygen: a randomized double-blind placebo controlled trial. *Undersea and Hyperbaric Medicine* 2004;**31**:Suppl.

* Clarke RE, Catalina Tenorio LM, Hussey JR, Toklu AS, Cone DL, Hinojosa JG, et al. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomised and controlled double-blind crossover trial with long-term follow-up. *International Journal of Radiation Oncology, Biology, Physics* 2008;**72**:134-43.

Forner 2022 *{published and unpublished data}*10.1016/j.radonc.2021.11.021

* Forner LE, Dieleman FJ, Shaw RJ, Kanatas A, Butterworth CJ, Kjeller G, et al. Hyperbaric oxygen treatment of mandibular osteoradionecrosis: combined data from the two randomized clinical trials DAHANCA-21 and NWHHT2009-1. *Radiotherapy and Oncology* 2022;**166**:137-44. [DOI: 10.1016/j.radonc.2021.11.021]

Glover 2016 *{published data only}*10.1016/S1470-2045(15)00461-1

Glover M, Smerdon GR, Andreyev HJ, Benton BE, Bothma P, Firth O, et al. Hyperbaric oxygen for patients with chronic bowel dysfunction after pelvic radiotherapy (HOT2): a randomised, double-blind, sham-controlled phase 3 trial. *Lancet Oncology* 2016;**17**:P224-33.

Gothard 2010 *{published data only}*10.1016/j.radonc.2010.04.026

* Gothard L, Haviland J, Bryson P, Laden G, Glover M, Harrison S, et al. Randomised phase II trial of hyperbaric oxygen therapy in patients with chronic arm lymphoedema after radiotherapy for cancer. *Radiotherapy and Oncology* 2010;**97**(1):101-7. [DOI: 10.1016/j.radonc.2010.04.026]

Hulshof 2002 *{published data only}*10.1007/s00066-002-0916-9

Hulshof M, Stark N, van der Kleij A, Sminia P, Smeding H, Gonzales D. Hyperbaric oxygen therapy for cognitive disorders after irradiation of the brain. *Strahlentherapie und Onkologie* 2002;**178**(4):192-8. [DOI: 10.1007/s00066-002-0916-9] [MEDLINE: 2002140155]

Marx 1985 *{published data only}*

Marx R, Johnson R, Kline S. Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. *Journal of the American Dental Association* 1985;**111**(1):49-54. [MEDLINE: 3897335]

Marx 1999a *{published data only}*

Marx R. Bony reconstruction of the jaw. In: Kindwall EP, Whelan HT, editors(s). Hyperbaric Medicine Practice. 2nd edition. Flagstaff (AZ): Best Publishing Company, 1999:460-3. [MEDLINE: 0-941332-78-0]

Marx 1999b *{published data only}*

Marx RE. Soft tissue flaps. In: Kindwall EP, Whelan HT, editors(s). Hyperbaric Medicine Practice. 2nd edition. Flagstaff (AZ): Best Publishing Company, 1999:464-8. [0-941332-78-0]

Oscarsson 2019 *{published data only}*10.1016/S1470-2045(19)30494-2

Oscarsson N, Muller B, Rosen A, Lodding P, Molne J, Giglio D, et al. Radiation-induced cystitis treated with hyperbaric oxygen therapy (RICH-ART): a randomised, controlled, phase 2–3 trial. *Lancet Oncology* 2019;**20**:1602-14. [DOI: 10.1016/S1470-2045(19)30494-2]

Oton Sanchez 2013 *{published data only}*10.1016/j.rpor.2013.03.842

Oton Sanchez C, Gonzalez Lugo Y, Oton Sanchez L, Diaz-flores Varela L, Jimenez Calero J, Puerto Romero P. Treatment of radiation-induced cervical fibrosis with pentoxifylline-tocoferol and hyperbaric oxygen. *Reports of Practical Oncology and Radiotherapy* 2013;**18**(S1):S111. [DOI: 10.1016/j.rpor.2013.03.842]

Pritchard 2001 *{published data only}*10.1016/s0167-8140(00)00319-4

* Pritchard J, Anand P, Broome J, Davis C, Gothard L, Hall E, et al. Double-blind randomized phase II study of hyperbaric oxygen in patients with radiation-induced brachial plexopathy. *Radiotherapy and Oncology* 2001;**58**(3):279-86. [DOI: 10.1016/s0167-8140(00)00319-4] [MEDLINE: 2001084162]

Yarnold J. Double-blind randomised phase II study of hyperbaric oxygen in patients with radiation-induced brachial plexopathy. *Radiotherapy and Oncology* 2005;**77**(3):327.

Schoen 2007 *{published data only}*10.1016/j.oraloncology.2006.04.009

Schoen PJ, Raghoebar GM, Bouma JA, Reintsema HA, Vissink AA, Sterk WA, et al. Rehabilitation of oral function in head and neck cancer patients after radiotherapy with implant-retained dentures: effects of hyperbaric oxygen therapy. *Oral Oncology* 2007;**43**(4):379-88. [DOI: 10.1016/j.oraloncology.2006.04.009]

Shao 2011 *{published data only}*10.1111/j.1464-410X.2011.10550.x

Shao Y, Lu G-L, Shen Z-J. Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. *BJU International* 2011;**109**:691-4. [DOI: 10.1111/j.1464-410X.2011.10550.x]

Shaw 2019 *{published data only}*10.1016/j.ijrobp.2019.02.044

Shaw R, Butterworth C, Tesfaye B, Bickerstaff M, Dodd S, Smerdon G, et al. HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): a randomised controlled trial of hyperbaric oxygen to prevent osteoradionecrosis of the irradiated mandible: study protocol for a randomised controlled trial. *Trials* 2018;**19**:22. [DOI: 10.1186/s13063-017-2376-7]

Shaw RJ, Butterworth CJ, Silcocks P, Tesfaye BT, Bickerstaff M, Jackson R, et al. HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): a randomized controlled trial of hyperbaric oxygen to prevent osteoradionecrosis of the irradiated mandible after dentoalveolar surgery. *International Journal of Radiation Oncology* 2019;**104**(3):530-9.

Sidik 2007 *{published data only}*10.24871/8120071-4

Sidik S, Daldiyono H, Setiabudy R, Gondowiardjo S, Yuwono V. Oxygen hyperbaric therapy in patients with radiation proctitis. *Indonesian Journal of Gastroenterology, Hepatology, and Digestive Endoscopy* 2007;**8**(1):1-4. [DOI: 10.24871/8120071-4]

Sidik S, Daldiyono H, Setiabudy R, Gondowiardjo S. Does hyperbaric oxygen administration decrease side effects and improve quality of life after pelvic irradiation? *Acta Medica Indonesiana* 2007;**39**(4):169-73.

Svalestad 2014 *{published data only}*10.1016/j.ijom.2013.07.006

Svalestad J, Hellem S, Thorsen E, Johannessen AC. Effect of hyperbaric oxygen treatment on irradiated oral mucosa: microvessel density. *International Journal of Oral and Maxillofacial Surgery* 2015;**44**:301-7.

* Svalestad J, Thorsen E, Vaagbø G, Hellem S. Effect of hyperbaric oxygen treatment on oxygen tension and vascular capacity in irradiated skin and mucosa. *International Journal of Oral and Maxillofacial Surgery* 2014;**43**:107-12. [DOI: 10.1016/j.ijom.2013.07.006]

Teguh 2009 *{published data only}*10.1016/j.ijrobp.2008.11.056

Teguh DN, Levendag PC, Noever I, Voet P, van der Est H, van Rooij P, et al. Early hyperbaric oxygen therapy for reducing radiotherapy side effects: early results of a randomized trial in oropharyngeal and nasopharyngeal cancer. *International Journal of Radiation Oncology, Biology, Physics* 2009;**75**(3):711-6. [DOI: 10.1016/j.ijrobp.2008.11.056]

References to studies excluded from this review

Carl 2001 *{published data only}*

Carl U, Feldmeier J, Schmitt G, Hartmann K. Hyperbaric oxygen therapy for late sequelae in women receiving radiation after breast-conserving surgery. *International Journal of Radiation Oncology Biology and Physics* 2001;**49**(4):1029-31. [MEDLINE: 11240244]

Coulthard 2002 *{published data only}*

Coulthard P, Esposito M, Worthington H, Jokstad A. Interventions for replacing missing teeth: hyperbaric oxygen therapy for irradiated patients who require dental implants. *Cochrane Database of Systematic Reviews* 2002, Issue 3. Art. No: CD003603. [DOI: 10.1002/14651858.CD003603]

Craighead 2011 *{published data only}*

Craighead, P, Shea-Budgell MA, Nation J, Esmail R, Evans AW, Parliament M, et al. Hyperbaric oxygen therapy for late radiation tissue injury in gynecologic malignancies. *Current Oncology* 2011;**18**(5):220.

Denton 2002 *{published data only}*

Denton A, Forbes A, Andreyev J, Maher E. Non surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis. *Cochrane Database of Systematic Reviews* 2002, Issue 1. Art. No: CD003455. [DOI: 10.1002/14651858.CD003455]

Gal 2003 *{published data only}*

Gal T, Yueh B, Futran N. Influence of prior hyperbaric oxygen therapy in complications following microvascular reconstruction for advanced osteoradionecrosis. *Archives of Otolaryngology – Head & Neck Surgery* 2003;**129**(1):72-6. [MEDLINE: 2003027602]

Granstrom 1999 *{published data only}*

Granstrom G, Tjellstrom A, Branemark P-I. Osseointegrated implants in irradiated bone: a case-controlled study using adjunctive hyperbaric oxygen therapy. *Journal of Oral and Maxillofacial Surgery* 1999;**57**:493-9. [0278-2391]

Maier 2000 *{published data only}*

Maier A, Gaggl A, Klemen H, Santler G, Anegg U, Fell B, et al. Review of severe osteoradionecrosis treated by surgery alone or surgery with postoperative hyperbaric oxygenation. *British Journal of Oral and Maxillofacial Surgery* 2000;**38**(3):173-6. [MEDLINE: 10864721]

Marson 2014 *{published data only}*

Marson F, Tienforte D, Kocjancic E. Post-radiation cystitis: current treatments. *Current Bladder Dysfunction Reports* 2014;**9**(3):156-60.

Niimi 1997 *{published data only}*

Niimi A, Fujimoto T, Nosaka Y, Ueda M. A Japanese multicenter study of osseointegrated implants placed in irradiated tissues: a preliminary report. *International Journal of Oral and Maxillofacial Implants* 1997;**12**(2):259-64. [MEDLINE: 9109278]

Rajaganapathy 2014 *{published data only}*

Rajaganapathy BR, Jayabalan N, Tyagi P, Kaufman J, Chancellor MB. Advances in therapeutic development for radiation cystitis. *LUTS: Lower Urinary Tract Symptoms* 2014;**6**(1):1-10.

Song 2018 *{published data only}*https://doi.org/10.1631/jzus.b1800132

Song KX, Liu S, Zhang MZ, Liang WZ, Liu H, Dong XH, et al. Hyperbaric oxygen therapy improves the effect of keloid surgery and radiotherapy by reducing the recurrence rate. *Journal of Zhejiang University* 2018;**19**(11):853-62.

Tobey 1979 *{published data only}*

Tobey R, Kelly J. Osteoradionecrosis of the jaws. *Otolaryngology Clinics of North America* 1979;**12**(1):183-6. [MEDLINE: 375158]

References to ongoing studies

Batenburg 2020 *{published data only}*10.1186/s13063-020-04869-z

Batenburg MC, van den Bongard HJ, Kleynen CE, Maarse W, Witkamp A, Ernst M, et al. Assessing the effect of hyperbaric oxygen therapy in breast cancer patients with late radiation toxicity (HONEY trial): a trial protocol using a trial within a cohort design. *Trials* 2020;**21**:980.

Bulsara 2019 *{published data only}*10.1136/bmjopen-2018-026662

Bulsara VM, Bulsara MK, Lewis E. Protocol for prospective randomised assessor-blinded pilot study comparing hyperbaric oxygen therapy with PENtoxifylline+TOcopherol± CLOdronate for the management of early osteoradionecrosis of the mandible. *BMJ Open* 2019;**9**(3):e026662.

NCT00087815 *{unpublished data only}*

NCT00087815. Hyperbaric oxygen therapy in treating patients with radiation necrosis of the brain. clinicaltrials.gov/study/NCT00087815 (first received 14 July 2004).

NCT02714465 *{unpublished data only}*

NCT02714465. Adverse radiation effects after gamma knife radio surgery and hyperbaric oxygen therapy (GKSHBO). clinicaltrials.gov/study/NCT02714465 (first received 1 March 2016).

NCT03144206 *{unpublished data only}*

NCT03144206. Evaluation of hyperbaric oxygen therapy on wound healing following management of soft tissue sarcoma with neo-adjuvant radiation and surgical resection. clinicaltrials.gov/study/NCT03144206 (first received 3 May 2017).

NCT03916068 *{unpublished data only}*

NCT03916068. Acute post-radiation hyperbaric oxygen (HBO2) for breast cancer patients who have recently completed radiation therapy. clinicaltrials.gov/study/NCT03916068 (first received 4 April 2019).

NCT04934644 *{unpublished data only}*

NCT04934644. The effect of hyperbaric oxygen treatment in patients with osteoradionecrosis. clinicaltrials.gov/study/NCT04934644 (first received 17 May 2021).

Additional references

ACS 2023

American Cancer Society. Cancer facts and figures 2021. www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2021.html (accessed 3 February 2023).

Baskar 2012

Baskar R, Lee KA, Yeo R, Yeoh KW. Cancer and radiation therapy: current advances and future directions. *International Journal of Medical Science* 2012;**9**(3):193-99. [DOI: 10.7150/ijms.3635] [PMID: 22408567]

Bennett 2011

Bennett M, Connor D. The database of randomised controlled trials in hyperbaric medicine. hboevidence.wikis.unsw.edu.au/ (accessed 23 June 2023).

Bennett 2019

Bennett MH, Hui CF, See HG, Au-Yeung KL, Tan C, Watson S. The myopic shift associated with hyperbaric oxygen administration is reduced when using a mask delivery system compared to a hood – a randomised controlled trial. *Diving and Hyperbaric Medicine* 2019;**49**(4):245-52. [DOI: 10.28920/dhm49.4.245-252]

Borab 2017

Borab Z, Mirmanesh MD, Gantz M, Cusano A, Pu LL. Systematic review of hyperbaric oxygen therapy for the treatment of radiation-induced skin necrosis. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 2017;**70**(4):529-38. [DOI: 10.1016/j.bjps.2016.11.024]

Camporesi 2014

Camporesi EM, Bosco G. Mechanisms of action of hyperbaric oxygen therapy. *Undersea & Hyperbaric Medicine* 2014;**41**(3):247-52.

Cardinal 2018

Cardinal J, Slade A, McFarland M, Keihani S, Hotaling JN, Myers JB. Scoping review and meta-analysis of hyperbaric oxygen therapy for radiation-induced hemorrhagic cystitis. *Current Urology Reports* 2018;**19**(38):1-8.

CEBM 2004 [Computer program]

CATmaker. Badenoch D, Sackett D, Straus S, Ball C, Dawes M, Version 1.1. Oxford (UK): Centre for Evidence Based Medicine, 2004.

Citrin 2010

Citrin D, Cotrim AP, Hyodo F, Baum BJ, Krishna MC, Mitchell JB. Radioprotectors and mitigators of radiation-induced normal tissue injury. *Oncologist* 2010;**15**(4):360-71.

Dalsania 2021

Dalsania RM, Shah KP, Stotsky-Himelfarb E, Hoffe S, Willingham FF. Management of long-term toxicity from pelvic radiation therapy. In: American Society of Clinical Oncology Educational Book. Vol. **41**. American Society for Clinical Oncology, 2021:147-57.

Drezner 2016

Drezner N, Hardy KK, Wells E, Vezina G, Ho CY, Packer RJ, et al. Treatment of pediatric cerebral radiation necrosis: a systematic review. *Journal of Neuro-Oncology* 2016;**130**:141-8. [DOI: 10.1007/s11060-016-2219-5]

Feldmeier 1995

Feldmeier JJ, Heimbach RD, Davolt DA, Court WS, Stegmann BJ, Sheffield PJ. Hyperbaric oxygen as an adjunctive treatment for delayed radiation injury of the chest wall: a retrospective review of twenty-three cases. *Undersea and Hyperbaric Medicine* 1995;**22**(4):383-93. [MEDLINE: 8574126]

Feldmeier 1998

Feldmeier JJ, Davolt DA, Court WS, Onoda JM, Alecu R. Histologic morphometry confirms a prophylactic effect for hyperbaric oxygen in the prevention of delayed radiation enteropathy. *Undersea and Hyperbaric Medicine* 1998;**25**(2):93-7. [MEDLINE: 9670434]

Feldmeier 2002

Feldmeier JJ, Hampson NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. *Undersea and Hyperbaric Medicine* 2002;**29**(1):4-30. [MEDLINE: 12507182]

Feldmeier 2003

Feldmeier J, Carl U, Hartmann K, Sminia P. Hyperbaric oxygen: does it promote growth or recurrence of malignancy? *Undersea and Hyperbaric Medicine* 2003;**30**(1):1-18. [MEDLINE: 12841604]

Feldmeier 2012

Feldmeier JJ. Hyperbaric oxygen therapy and delayed radiation injuries (soft tissue and bony necrosis): 2012 update. *Undersea and Hyperbaric Medicine* 2012;**39**(6):1121-39.

Flannigan 2014

Flannigan RK, Baverstock RJ. Management of post-radiation therapy complications among prostate cancer patients: a case series. *Canadian Urological Association Journal* 2014;**8**(9-10):E632.

Fox 2015

Fox NF, Xiao C, Sood AJ, Lovelace TL, Nguyen SA, Sharma A, et al. Hyperbaric oxygen therapy for the treatment of radiation-induced xerostomia: a systematic review. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 2015;**120**(1):22-8.

Hadanny 2020

Hadanny A, Efrati S. The hyperoxic–hypoxic paradox. *Biomolecules* 2020;**10**(6):958.

Hampson 2012

Hampson NB, Holm JR, Wreford-Brown CE, Feldmeier J. Prospective assessment of outcomes in 411 patients treated with hyperbaric oxygen for chronic radiation tissue injury. *Cancer* 2012;**118**:3860-8.

Helmers 2022

Helmers R, Milstein DM, Straat NF, Navran A, Teguh DN, van Hulst RA, et al. The impact of hyperbaric oxygen therapy on late irradiation injury in oral microcirculation. *Head & Neck* 2022;**44**(7):1646-54. [DOI: 10.1002/hed.27073]

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Higgins 2021

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s) Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. training.cochrane.org/handbook/archive/v6.2.

Hills 1999

Hills BA. A role for oxygen-induced osmosis in hyperbaric oxygen therapy. *Medical Hypotheses* 1999;**52**:259-63.

Hoggan 2014

Hoggan BL, Cameron AL. Systematic review of hyperbaric oxygen therapy for the treatment of non-neurological soft tissue radiation-related injuries. *Supportive Care in Cancer* 2014;**22**(6):1715-26.

IARC 2020

The Global Cancer Observatory. All cancers fact sheet. gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf (accessed 4 October 2021).

Jain 2017

Jain KK. Textbook of Hyperbaric Medicine. Sixth edition. Basel (Switzerland): Springer International Publishing AG, 2017.

Jokinen-Gordon 2017

Jokinen-Gordon H, Barry R, Watson B, Covington D. A retrospective analysis of adverse events in hyperbaric oxygen therapy (2012–2015): lessons learned from 1.5 million treatments. *Advances in Skin & Wound Care* 2017;**30**(3):125-9. [DOI: 10.1097/01.ASW.0000508712.86959.c9.]

Mainous 1975

Mainous EG, Hart GB. Osteoradionecrosis of the mandible. Treatment with hyperbaric oxygen. *Archives of Otolaryngology* 1975;**101**(3):173-7. [MEDLINE: 804303]

Majeed 2022

Majeed H, Gupta V. Adverse Effects of Radiation Therapy. Treasure Island (FL): StatPearls Publishing, 2021.

Marx 1983

Marx RE. A new concept in the treatment of osteoradionecrosis. *Journal of Oral and Maxillofacial Surgery* 1983;**41**:351-7.

Marx 1988

Marx RE, Johnson RP. Problem wounds in oral and maxillo-facial surgery: the role of hyperbaric oxygen. In: Davis JC, Hunt TK, editors(s). Problem Wounds: the Role of Oxygen. New York (NY): Elsevier, 1988:65-123.

Marx 1990

Marx RE, Ehler WJ, Tayapongsak P. Relationship of oxygen dose to angiogenesis induction in irradiated tissue. *American Journal of Surgery* 1990;**160**:519-24.

Mathieu 2006

Mathieu D. Handbook on Hyperbaric Medicine. 1st edition. Dordrecht (the Netherlands): Springer, 2006.

Neuman 2008

Neuman T, Thom S. Physiology and Medicine of Hyperbaric Oxygen Therapy. 1st edition. Philadelphia (PA): Saunders, 2008.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analysis of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**:2815-34.

Ravi 2017

Ravi P, Vaishnavi D, Gnanam A, Raja VB. The role of hyperbaric oxygen therapy in the prevention and management of radiation-induced complications of the head and neck – a systematic review of literature. *Journal of Stomatology, Oral and Maxillofacial Surgery* 2017;**118**(6):359-62.

RevMan 2020 [Computer program]

Review Manager (RevMan). Version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html.

Shah 2017

Shah DN, Chauhan CJ, Solanki JS. Effectiveness of hyperbaric oxygen therapy in irradiated maxillofacial dental implant patients: a systematic review with meta-analysis. *Journal of Indian Prosthodontic Society* 2017;**17**(2):109-19. [DOI: 10.4103%2F0972-4052.203193]

Stone 2003

Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissue: consequences and mechanisms. *Lancet Oncology* 2003;**4**(9):529-36. [MEDLINE: 12965273]

Thompson 1999

Thompson IM, Middleton RG, Optenberg SA, Austenfeld MS, Smalley SR, Cooner WH, et al. Have complication rates decreased after treatment for localized prostate cancer? *Journal of Urology* 1999;**162**(1):107-12. [MEDLINE: 10379751]

Villeirs 2019

Villeirs L, Tailly T, Ost P, Waterloos M, Dacaestecker K, Fonteyne V, et al. Hyperbaric oxygen therapy for radiation cystitis after pelvic radiotherapy: systematic review of the recent literature. *International Journal of Urology* 2019;**27**(2):98-107. [DOI: 10.1111/iju.14130]

Whelan 2017

Whelan HT, Kindwall EP. Hyperbaric Medical Practice. 4th edition. North Palm Beach (FL): Best Publishing Company, 2017.

Yuan 2009

Yuan J, Handy RD, Moody AJ, Bryson P. Response of blood vessels in vitro to hyperbaric oxygen (HBO): modulation of VEGF and NO_X release by external lactate or arginine. *Biochimica et Biophysica Acta (BBA) - Bioenergetics* 2009;**1787**(7):828-34.

Yuan 2020

Yuan J, Song L, Liu Y, Li M, Lin Q, Wang R, et al. The effects of hyperbaric oxygen therapy on pelvic radiation induced gastrointestinal complications (rectal bleeding, diarrhea, and pain): a meta-analysis. *Frontiers in Oncology* 2020;**10**:390.

References to other published versions of this review

Bennett 2005

Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No: CD005005. [DOI: 10.1002/14651858.CD005005.pub2]

Bennett 2012

Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database of Systematic Reviews* 2012, Issue 5. Art. No: CD005005. [DOI: 10.1002/14651858.CD005005.pub3]

Bennett 2016

Bennett MH, Feldmeier J, Hampson NB, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database of Systematic Reviews* 2016, Issue 4. Art. No: CD005005. [DOI: 10.1002/14651858.CD005005.pub4]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Annane 2004

Study characteristics	
Methods	**Study design:** multicentre RCT with central computerised allocation concealment and participant/outcome assessor blinding
Participants	People with overt ORN for ≥ 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

Annane 2004 *(Continued)*

	HBOT: 100% oxygen on same schedule
Outcomes	Resolution of the problem, establishment of mucosal cover
Notes	Study 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
Random sequence generation (selection bias)	Low risk	Clear description. Quote: "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	Quote: "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. Quote: "HBO 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. Quote: "HBO 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	Quote: "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. (Quote): "Among the 68 randomly assigned patients, at 1 year there were six (19.3%) of 31 patients who had recovered in the HBO 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

Study characteristics	
Methods	**Study design:** 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; 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	Quote: "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 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. Quote: "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. Quote: "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. Quote: "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	Quote: "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. Quote: "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

Clarke 2008 *(Continued)*

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.

Forner 2022

Study characteristics	
Methods	**Study design:** RCT **Setting:** pooled data from DAHANCA-21 (Denmark, 1 site), (Sweden, 1 site), (UK, 5 sites) – 77 participants and NWHHT2009-1 (Netherlands, 5 sites) – 20 participants
Participants	**Criteria for defining the condition being treated:** aged > 18 years with ORN of the mandible requiring surgical removal of necrotic bone after RT for head and neck cancer (any site) **Exclusion criteria (not listed above):** previous HBOT, had active cancer or contraindications to HBO such as a pneumothorax, uncontrolled hypertension, uncontrolled epilepsy or claustrophobia that could not be treated with medication **Baseline characteristics:** in DAHANCA-21, participants were stratified according to ORN grade and centre. Participants in NWHHT2009-1 were not stratified. Recorded treatment centre, sex, age, smoking, BMI, pain, dental status, baseline ORN, surgical procedure and number of HBO treatments **Overall cohort** Number of participants at enrolment: 97 Number randomised: 97 Number included in analyses: 65 Age: median 61 (range 49–80) years Sex: 55 men, 10 women Diagnosis: ORN ORN grades: Grade 0 (3 participants), Grade 1 (7), Grade 2 (11), Grade 3 (28), Grade 4 (5), unknown grade (11) **Group 1: surgery** Number of participants at enrolment: 51 Number randomised: 51 Number included in analyses: 35 Age: median 61 (range 49–80) years Sex: 30 men, 5 women Diagnosis: ORN ORN grades: Grade 0 (2 participants), Grade 1 (4), Grade 2 (9), Grade 3 (12), Grade 4 (3), unknown grade (5) **Group 2: HBOT and surgery**

Forner 2022 *(Continued)*

	Number of participants at enrolment: 46 Number randomised: 46 Number included in analyses: 30 Age: median 60 (range 51–78) years Sex: 25 men, 5 women Diagnosis: ORN ORN grades: Grade 0 (1 participant), Grade 1 (3), Grade 2 (2), Grade 3 (16), Grade 4 (2), unknown grade (6) Treatment history: 26/30 participants received full 40 treatments
Interventions	Participants were randomly assigned (1:1) to receive or not to receive HBO supplemental to surgical removal of necrotic mandibular bone. **Control:** surgery only **HBOT + surgery:** 100% oxygen was individually delivered through a hood or tight-fitting mask in a pressurised room at 243 kPa (2.4 ATA) for 90 minutes in 40 daily sessions 5 days a week (30 pre- and 10 postoperative) delivered over a period of 6 and 2 weeks respectively. **Co-interventions** Surgery was performed according to the extent of the bone necrosis, as judged by the treating clinician. Small necrotic lesions were treated by removal of small sequesters, while larger necrotic lesions were treated with larger resections with or without discontinuation of the mandible. Some participants with discontinuation of the mandible were reconstructed with a free vascularised bone graft. Differences in frequencies (1 year after surgery) of participants healed were evaluated using the Chi^2 test and expressed as odds ratios.
Outcomes	**Outcomes included in the review** **Outcome 1: healing at 12 months** Surgery alone: 18/35 (51%) HBOT and surgery 21/30 (70%) Odds ratio 2.2 (95% CI 0.7 to 7); P = 0.13 **Outcome 2: improvement of ADL Score at 12 months** Surgery alone: no improvement: 17 (59%) participants HBOT and surgery 19 (79%) participants **Outcome 3: pain – VAS** **3 months:** −10.6% change (95% CI −32.6 to 11.3) mean difference between HBOT + surgery and surgery only groups **12 months:** −6.1% change (95% CI −27.9 to 15.8) mean difference between HBOT + surgery and surgery only groups Data from graph in supplementary word document – extracted with webplotdigitizer apps.automeris.io/wpd/ **Pain score at 12 months (out of 10)** HBOT (30 participants): mean 2.17, 95% CI 1.04 to 3.27

Forner 2022 *(Continued)*

	SD (calculated): 5.48 × 2.23/3.92 = 3.12 No HBOT (35 participants): mean 2.51, 95% CI 1.54 to 3.45 SD (calculated) = 5.92 × 1.91/3.92 = 2.88 **Outcomes also reported** Xerostomia, unstimulated whole saliva floor rate, dysphagia QoL: EORTC QLQ-C30 and EORTC QLQ-H&N35 Pain assessment (analgesics consumption) and smoking habits Xerostomia (UKU-SERS) + unstimulated whole saliva
Notes	Danish Cancer Society, National Institute for Health Research (NIHR) infrastructure at Leeds (DenT-CRU|), Danish Cancer Research foundation, Danish Dental Association, Doctor Sofus Carl Emil and Wife Olga Doris Friis Foundation, Research funding support from Cancer Research UK in Liverpool Trials unit in co-ordinating UK data. UK National Cancer Research Institute. DAHANCA-21: ethics by Regional Ethics Committee of the Capital Region of Denmark (H-A-2008-031) – Danish Medicines Health Agency – EudraCT no. 2007-007842-36 NWHHT2009-1: ethics approval by the Dutch Central Committee on Research Involving Human Subjects (CCMO NL20963.091.08 EudraCT no. 2008-001972-55)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were randomly assigned (1:1) to receive or not to receive HBO supplemental to surgical removal of necrotic mandibular bone. No mention of randomisation method.
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned (1:1) to receive or not to receive HBO supplemental to surgical removal of necrotic mandibular bone. In DAHANCA-21, participants were stratified according to ORN grade and centre. Participants in NWHHT2009-1 were not stratified.
Blinding (performance bias and detection bias) All outcomes	High risk	Allocation of treatment was unblinded to participants and investigators.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Allocation of treatment was unblinded to participants and investigators.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Allocation of treatment was unblinded to outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Minimal raw data published, mostly univariate/multivariate analyses and MD processed data after treatment.
Selective reporting (reporting bias)	Low risk	clinicaltrials.gov/ct2/show/NCT00760682

Forner 2022 *(Continued)*

		DAHANCA-21 protocol reviewed, most outcomes reported as suggested in protocol – no reported trismus data.
Other bias	Low risk	None noted

Glover 2016

Study characteristics	
Methods	**Study design:** double-blind, sham-controlled, phase 3 RCT **Setting:** 10 UK hyperbaric medicine facilities registered with British Hyperbaric Association.
Participants	**Criteria for defining the condition being treated:** men/women aged ≥ 18 years with ≥ grade 2 gastrointestinal symptoms in any category of the late effects normal tissue scoring system (LENT SOMA); no cancer recurrence Symptoms attributed to RT: had 3 months of optimum standard treatment including antibiotic treatment for small bowel overgrowth, bile acid malabsorption, lifestyle advice and supervised by gastroenterologist – must have been unsuccessful **Any restriction on duration of symptoms:** ≥ 3 months of treatment prior – radiation injury for 12 months prior **Inclusion criteria (not listed above):** – **Exclusion criteria (not listed above):** medical history of cancer recurrence, rectal surgery, previous HBOT (except treatment for decompression illness) exposure to bleomycin, claustrophobia, epilepsy, uncontrolled asthma, bullous lung disease, some ear surgery, inability to equalise middle ear, history of prostate of cancer **Baseline characteristics** **Overall cohort of participants** Number of participants at enrolment: 84 (from 241 screened) Number randomised: 84 Number included in analyses: 26 (sham control ITT), 48 (HBOT ITT) 25 (sham control per protocol), 40 (HBOT per protocol) 22 (sham bowel component), 11 (sham rectal bleeding), 38 (HBOT bowel component), 25 (HBOT rectal bleeding) **Group 1: sham control** Number of participants at enrolment: 29 Number randomised: 29 Number included in analyses: 26 (ITT) (25 per protocol) – 22 bowel component, 11 rectal bleeding Age: mean 62, median 63.7 (IQR 53.6–69.9), range 37.3–79.3 years Sex: 14 (48%) men, 15 (52%) women Diagnosis: prostate 12 (41%), anus 4 (14%), vagina 3 (10%), cervix 5 (17%), uterus 3 (10%), other (anal canal/vulva) 2 (7%) Duration of symptoms: median 3.9 years (IQR 2.5–5.7) since pelvic RT, range 1.5–21.2 years

Glover 2016 *(Continued)*

	Treatment history: 3 months of optimum standard treatment including antibiotic treatment for small bowel overgrowth, bile acid malabsorption, lifestyle advice, supervised by gastroenterologist – must have been unsuccessful **Group 2: HBOT** Number of participants at enrolment: 55 Number randomised: 55 Number included in analyses: 48 (ITT) 40 per-protocol population – 38 (bowel component) 25 (rectal bleeding) Age: mean 62.3, median 63.7 (IQR 53.9–71.2), range 34.5–80.9 years Sex: men 23 (42%), women 32 (58%) Diagnosis: prostate 21 (38%), anus 4 (7%), vagina 1 (2%), cervix 17 (31%), uterus 8 (15%), retroperitoneum 1 (2%), pelvis 1 (2%), rectum 1 (2%), bladder 1 (2%) Duration of symptoms: pelvic RT median 3.5 years (IQR 2.3–9.7), range (1.2–34) years Treatment history: had 3 months of optimum standard treatment including antibiotic treatment for small bowel overgrowth, bile acid malabsorption, lifestyle advice, supervised by gastroenterologist – must have been unsuccessful **Pretreatment group differences:** 2:1 ratio of HBOT:sham control Small imbalance in proportion of reporting a medical history of rectal bleeding at trial entry
Interventions	**Sham control:** 40 pressure exposures at 1.3 ATA (131 kPa) breathing 21% oxygen for 90 minutes with 2 simulated 5-minute air breaks **HBOT:** 40 pressure exposures at 2.4 ATA (243 kPa), 100% oxygen for 90 minutes with 5-minute air breaks at 30-minute intervals
Outcomes	**Outcomes included in the review** Trial ended at 12 months from start of treatment **Outcome 1: IBDQ – Bowel Function (higher scores signify improvement of symptoms)** Baseline: sham (23 participants): median 51 (IQR 44–59), HBOT (46 participants) median 48 (IQR 42–52) Measured at time point 12 months: sham: median 53 (IQR 40–59), HBOT median 51 (IQR 36–62) Median change: sham: median 4 (IQR −6 to 90), HBOT 3.5 (−3 to 11): Mann Whitney score 0.67, P = 0.5 Calculations of data for meta-analysis entry Median approximated to mean assuming normal distribution, SD = IQR/1.35 MD: sham 4 (SD 71.1), HBOT 3.5 (SD 10.4) **Outcome 2: IBDQ – Rectal Bleeding (higher scores signify improvement of symptoms)** Baseline: sham (11 participants): median 3 (IQR 2–4), HBOT (29 participants) median 3 (IQR 2–4) Measured at time point 12 months: sham: median 4 (IQR 2–6), HBOT median 6 (IQR 3–7) Median change: sham 1 (IQR 1 to 2), HBOT 3 (IQR 1 to 3); Mann Whitney score 1.69, P = 0.092 Calculations of data for meta-analysis entry Median approximated to mean assuming normal distribution, SD = IQR/1.35

Glover 2016 *(Continued)*

MD: sham 1 (SD 0.74), HBOT 3 (SD 11.48)

Outcome 3: LENT-SOMA Rectum at 12 months

Baseline: sham (26 participants): median 6 (IQR 5–8), HBOT (46 participants): median 6 (IQR 4–8)

Measured at time point 12 months: sham: median 4.5 (IQR 2–8), HBOT median 5 (IQR 3–8)

Median change: sham: median 1.5 (IQR −4 to 0), HBOT −1 (−2 to 1); Mann Whitney score 1.56, P = 0.12

Calculations of data for meta-analysis entry

Median approximated to mean assuming normal distribution, SD = IQR/1.35

MD: sham 1.5 (SD 2.96), HBOT −1 (SD 2.22)

Outcome 4: LENT-SOMA Intestine at 12 months

Baseline: sham (26 participants): median 2.5 (IQR 1–4), HBOT (46 participants): median 4 (2–5)

Measured at time point 12 months: sham: median 1 (IQR 1–4), HBOT 2.5 (IQR 1–4)

Median change: sham: 0 (IQR −1 to 1), HBOT 0 (−2 to 0); Mann Whitney score −1.30, P = 0.20

Calculations of data for meta-analysis entry

Median approximated to mean assuming normal distribution, SD = IQR/1.35

MD: sham 0 (SD 1.48), HBOT 0 (SD 1.48)

Outcome 5: adverse effects

Myopia: sham 3/28 (11%), HBOT 16/53 (30%)

Fatigue: sham 3/28 (11%), HBOT 2/53 (4%)

Ear pain/barotrauma: sham 6/28 (21%), HBOT 15/53 (28%)

Outcome 6: serious adverse events

Sham: 2 participants had tonsillitis or recurrent cancer of the vulva

HBOT: 6 participants had malignant spinal cord compression, malignant para-aortic lymph node involvement requiring surgery, recurrence of vomiting and dehydration, diarrhoea and fever from campylobacter infection, recurrence of abdominal pain, bloating, diarrhoea, and urinary tract infection. All thought to be unrelated to treatment

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants were randomly assigned (2:1) to receive HBOT or sham. Randomisation was arranged by a telephone call from Hyperbaric Medicine Facility to Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU). Randomisation was computer-generated random permuted blocks (block size of 9 and 12) and participants were stratified by centre. Computer-generated lists were used to allocate participants within a block.
Allocation concealment (selection bias)	Low risk	Only engineers and technicians were informed of the allocated treatment by the trials office. Participants, clinicians, nurse practitioners and other healthcare professionals associated with participants' care remained masked to

Glover 2016 *(Continued)*

		treatment allocation. Non-trial patients did not share chamber with a trial participant.
Blinding (performance bias and detection bias) All outcomes	Low risk	Only engineers and technicians were informed of the allocated treatment by the trials office. Participants, clinicians, nurse practitioners and other health-care professionals associated with participants' care remained masked to treatment allocation. Non-trial patients did not share chamber with a trial participant.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Only engineers and technicians were informed of the allocated treatment by the trials office. Participants, clinicians, nurse practitioners and other health-care professionals associated with participants' care remained masked to treatment allocation. Non-trial patients did not share chamber with a trial participant.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were not informed of their treatment allocation and were to complete 2 separate scoring sheets at time intervals of the same scale. IBDQ and LENTSOMA Scale Non-trial patients did not share chamber with a trial participant.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis was performed as per-protocol basis. 84 were enroled and randomised and 74 were analysed in ITT population, this was later reduced to 65 as per-protocol analysis based on compliance. The study authors compared both analysis and found no difference between per-protocol and ITT analysis.
Selective reporting (reporting bias)	Low risk	The RCT reported negative data results as compared to other positive trials. Furthermore, all data were reported as per-protocol analyses.
Other bias	Low risk	Study authors declared no competing interests.

Gothard 2010

Study characteristics	
Methods	**Study design:** 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 ≥ 3 months with good treatment for lymphoedema
Interventions	**Control:** 'good standard care' for lymphoedema **HBOT + standard care:** 'good standard care' for lymphoedema + HBOT at 2.4 ATA with 90 minutes of 100% oxygen breathing for a total of 30 treatment sessions over 6 weeks
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:

Gothard 2010 *(Continued)*

		Quote: "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 Quote: "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. Quote: "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	No blinding and 1 of the main outcomes was QoL. Bias less likely for arm volume and other objective outcomes. Quote: "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 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. Quote: "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 of selective reporting.
Other bias	Low risk	No indication of other bias.

Hulshof 2002

Study characteristics	
Methods	**Study design:** RCT using random number table with allocation concealment but no blinding. Randomised in matched pairs
Participants	7 people with cognitive deficits presented ≥ 1.5 years after irradiation of the brain with ≥ 3000 cGy
Interventions	**Control:** no specific treatment **HBOT:** 100% oxygen at 3 ATA for 115 minutes for 30 sessions over 6 weeks (5/7 days each week)
Outcomes	Neuropsychiatric testing
Notes	Very low power study with many outcomes

Hulshof 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The actual method used was unclear. Quote: "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. Quote: "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 reported. Quote: "All seven eligible patients completed the full period of 30 HBO 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. Quote: "The immediate group consisted of four patients and the delayed group of three patients."

Marx 1985

Study characteristics

Methods	**Study design:** multicentre randomised trial. No details of methodology for randomisation, allocation concealment or blinding
Participants	74 people requiring tooth extraction in a field irradiated with ≥ 6000 cGy > 6 months and < 15 years previously Exclusion criteria: penicillin or HBOT contraindications, active tumour present, recent chemotherapy or concurrent disease (e.g. diabetes) that might affect wound healing

Marx 1985 *(Continued)*

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 **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

Study characteristics

Methods	**Study design:** described as randomised. No details concerning blinding or allocation concealment
Participants	104 people requiring hemi-mandibular jaw reconstruction in tissue beds exposed to ≥ 6400 cGy RT. 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

Marx 1999a *(Continued)*

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	Incomplete account within a textbook chapter written by the study 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."
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

Study characteristics	
Methods	**Study design:** 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	Incomplete account within a textbook chapter written by the study author

Marx 1999b *(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.

Oscarsson 2019

Study characteristics

Methods	**Study design:** phase 2–3 RCT **Setting:** 5 Nordic university hospitals (Gothenburg and Stockholm in Sweden, Bergen in Norway, Copenhagen in Denmark and Turku in Finland)
Participants	**Criteria for defining the condition being treated:** persistent symptoms with a score < 80 in the EPIC Urinary domain and referred to hyperbaric for symptoms of late radiation cystitis **Any restriction on duration of symptoms:** ≥ 6 months after intended curative RT **Inclusion criteria (not listed above):** men or women aged 18–80 years, late radiation cystitis assessed by urologist **Exclusion criteria (not listed above):** ongoing bleeding requiring blood transfusions > 500 mL in 4 weeks, permanent urinary catheter, bladder capacity < 100 mL, fistula in the urinary bladder, previous hyperbaric treatment for late radiation injuries and contraindications to hyperbaric treatment **Baseline characteristics** **Overall cohort of participants** Number of participants at enrolment: 87 enroled and randomised (of 223 screened)

Oscarsson 2019 *(Continued)*

Number randomised: 87

Number included in analyses: 79

Group 1: HBOT

Number of participants at enrolment: 42

Number randomised: 42; 1 withdrew consent

Number included in analyses: 41; 1 discontinued due to adverse event, 40 as per-protocol analysis

Age: mean 64 (SD 13.6) years

Sex: 29 (71%) men, 12 (29%) women

Smoking status: 2 (5%), other nicotine use 3 (7%)

Previous invasive surgery: 19 (46%)

Diagnosis: cervix 10 (24%), prostate 27 (66%), rectum 3 (7%), other 1 (2%)

Time from RT to inclusion: mean 4.4 (SD 5.1) years

Duration of symptoms: mean 3.1 (SD 4.8) years

Treatment history: external radiation dose: mean 63.8 (SD 12.2) Gy, brachytherapy 12 (29%) participants; mean 21 (SD 6.5) Gy, 10 participants

Total combined radiation dose: mean 79.5 (SD 8.8) Gy, 10 participants

Concurrent treatment: chemotherapy 12 (29%) participants

Group 2: standard care

Number of participants at enrolment: 45

Number randomised: 45, 7 withdrew consent

Number included in analyses: 38, 4 died so 34 as per-protocol analysis

Age: mean 68 (SD 10.7) years

Sex: 28 (74%) men, 10 (26%) women

Smoking status 5 (13%), other nicotine use 2 (5%)

Previous invasive surgery: 19 (50%)

Diagnosis: cervix 8 (21%), prostate 27 (71%), rectum 0, uterus 2 (5%), other 1 (3%)

Time from RT to inclusion: mean 4.1 (SD 3.4) years

Duration of symptoms: mean 2.8 (SD 2.8) years

Treatment history: external radiation dose mean 63.5 (SD 10.7) Gy, Brachytherapy 13 (34%) participants mean 18.2 (SD 5.2) Gy, 12 participants

Total combined radiation dose: mean 69.1 (SD 9.5) Gy, 12 participants

Concurrent treatment: chemotherapy 14 (37%)

Pretreatment group differences: small difference in EPIC Scores HBOT: mean 48.2 (SD 19) vs standard care: mean 41.6 (SD 17.2); P = 0.11

Interventions	**HBOT:** 100% oxygen at 240–250 kPa for 80–90 minutes 5 times a week for 30–40 sessions

Oscarsson 2019 *(Continued)*

Control: standard treatment

Co-interventions: ongoing standard treatment for radiation cystitis by Urologists

Outcomes

Outcomes included in the review

Time frame: 6–8 months after randomisation – (visit 4) – after completion, all standard care participants were offered HBOT

Discontinuation: patient discretion, new cancer, incorrect enrolment, complications to HBOT, and for other conditions

Measurements based on ITT population

Measured at time points: visit 4–6 to 8 months after commencement of treatment

Primary outcome 1: absolute change in EPIC Urinary Total Score[a]

Urinary Total

Hyperbaric group (40 participants) – mean increase 17.8 (SD 18.4) points

Standard treatment (35 participants) – mean increase 7.7 (SD 15.5) points

ITT analysis: MD 10.1 points (95% CI 2.2 to 18.1; P = 0.013), adjusted mean 10.4 (95% CI 2.3 to 18.5; P = 0.012)

Per-protocol analysis: MD 11.4 points (95% CI 3.5 to 19.2; P = 0.0047)

Outcome 1a: absolute change in EPIC Bowel Total Score[a]

Hyperbaric group: mean increase 13.2 (SD 17.3) points

Standard treatment: mean increase 4.9 (SD 12.7) points

Per-protocol analysis: MD 8.33 points (95% CI 1.15 to 15.54; P = 0.024)

Outcome 2: changes in SF-36 total and domain scores[a]

Physical Functioning

HBOT: mean 4.6 (SD 13.8), standard care: mean −1.6 (SD 15.0); MD 6.19 (95% CI −0.49 to 12.87; P = 0.075)

Role Limitations due to Physical Health

HBOT: mean 12.2 (SD 48.6), standard care: mean −2.1 (SD 34.0); MD 14.3 (95% CI −5.1 to 33.9; P = 0.15)

Role Limitations due to Emotional Problems

HBOT: mean −5.1 (SD 46.2), standard care: mean −3.8 (SD 47.7); MD −1.32 (95% CI −23.10 to 20.46; P = 0.9)

Energy/Fatigue

HBOT: mean 7.2 (SD 18.4), standard care: mean 1.1 (SD 14.4); MD 6.04 (95% CI −1.65 to 13.72; P = 0.13)

Emotional Wellbeing

HBOT: mean 3.8 (SD 18.1), standard care: mean 0.6 (SD 13.3); MD 3.22 (95% CI −4.19 to 10.64; P = 0.41)

Social Functioning

HBOT: mean 5.4 (SD 26.7), standard care, mean −0.357 (SD 21.964); MD 5.81 (95% CI −5.62 to 17.14; P = 0.32)

Pain

Oscarsson 2019 *(Continued)*

HBOT: mean 8.3 (SD 23.7), standard care: mean 7.1 (SD 22.9); MD 1.19 (95% CI −9.67 to 12.04; P = 0.85)

General Health

HBOT: mean 9.4 (SD 16.5), standard care: mean −3.9 (SD 14.3); MD 13.2 (95% CI 6.0 to 20.4; P = 0.0006)

Outcome 3: histological changes in urinary bladder biopsies

Published separately

Outcome 4: LRMGS Grades (Radiation Therapy Oncology Group grades)

Visit 1: HBOT vs standard care: higher scores in HBOT group (P = 0.068)

Visit 4: HBOT: 25/39 (64%) improved grades, 11/39 (28%) unchanged, 3/39 (8%) worsened grades; standard care: 6/34 (18%) improved grades, 18/34 (53%) unchanged, 10/34 (29%) worsened grades; Mantel-Haenszel Chi^2 test P = 0.0012

Outcome 5: adverse events

HBOT: 17/41 (41%) participants; 9 events from failure to equalise pressure in middle ear in 6 participants (15%)

HBOT: 441 (10%) participants had barotrauma requiring paracentesis of tympanic membrane in 1/41 (2%) participants

Hyperbaric-induced myopia recorded in 5 (12%) participants

[a]Answers are given on Likert scales that are transformed to a 0 to 100 score, in which a lower value indicates more severe symptoms

Notes

All Interventions extracted for this review, and those not extracted as not relevant

All outcomes extracted for the review, pending data from histology samples

Time points extracted for this review: visit 4–6 to 8 months after treatment

Outcomes that could not be extracted: histology samples, not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned in 1:1 ratio to receive either HBOT or standard care. Allocation was computer generated with block sizes of 4 for each stratification group. Randomisation was stratified by sex, time from RT and previous invasive surgery in the pelvis.
Allocation concealment (selection bias)	Low risk	The investigators had no possibility to influence the randomisation, nor to change the allocated group. Randomisation was stratified by sex (male vs female), time from RT to inclusion (≥ 12 months vs < 12 months), and previous invasive surgery in the pelvic area, defined as either pelvic surgery for malignant disease or surgery to the lower urinary tract for any reason (yes vs no).
Blinding (performance bias and detection bias) All outcomes	High risk	No attempt was made to mask participants or investigators to the allocated intervention.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded to treatment arm. Subjective outcomes are given in a scale and combined to form the EPIC score but a large number of subjective outcomes suggest detection bias in context of non-blinding.

Oscarsson 2019 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Final grade of cystoscopy findings determined by a blinded and independent examiner using a transcript of urologist reports.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data to be published for secondary outcomes. All stated protocol primary outcomes published. 87 randomised participants with 74 included in per-protocol analysis with a fairly balanced groups of 40:34 from 42:45 and a mentioned ITT analysis of 41:38.
Selective reporting (reporting bias)	Low risk	Commitment of data to be published for secondary outcomes. All stated protocol primary outcomes published.
Other bias	Low risk	Board member in MediCase AB in 2014.

Oton Sanchez 2013

Study characteristics		
Methods	**Study design:** 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	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) + pentoxifylline 400 mg and tocopherol 400 mg twice daily for 6 months Control: pentoxifylline 400 mg and tocopherol 400 mg twice daily for 6 months	
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. Quote: "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.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "An open, controlled, randomized clinical trial."

Oton Sanchez 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "37 patients were randomised and 26 completed the trial." None of the missing participants 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

Study characteristics	
Methods	**Study design:** 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	**HBOT:** 100% oxygen breathing on the same schedule **Control:** 100 minutes at 2.4 ATA breathing 41% oxygen to simulate 100% oxygen at 1 ATA, daily 5 days per week for 30 sessions
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	Quote: "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	Quote: "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	Quote: "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	Quote: "Individuals allocated to the control group accompanied the HBO_2 group patients and experienced the same number and type of pressure exposures."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "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)	Low risk	Quote: "Only 1/72 assessments over 12 months of planned follow up was missed."

Pritchard 2001 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other significant bias detected.

Schoen 2007

Study characteristics		
Methods	**Study design:** 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 17 males, 9 females	
Interventions	**HBOT:** 20 sessions on 100% oxygen at 2.5 ATA for 80 minutes daily before operation and for 10 days after operation + perioperative antibiotics **Control:** perioperative antibiotics	
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	Quote: "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. Quote: "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 were subjective (e.g. QoL). Quote: "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 were subjective (e.g. QoL). Quote: "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. Quote: "All clinical assessments were performed by the investigator (PJS) who was not involved in treatment of the patients."
Incomplete outcome data (attrition bias)	High risk	Significant losses to follow-up.

Schoen 2007 *(Continued)*

All outcomes		Quote: "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 related 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)	Low risk	No indication that outcome measures have not been reported.
Other bias	Low risk	No indication of other bias.

Shao 2011

Study characteristics	
Methods	**Study design:** 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 for 30 treatments **Control:** 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	Quote: "We used computer-generated random numbers to perform the randomisation."
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment.
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.

Shao 2011 *(Continued)*

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.
Other bias	Low risk	No other major source of bias identified.

Shaw 2019

Study characteristics	
Methods	**Study design:** Phase 3 RCT **Setting:** 16 acute UK hospitals, 1 acute hospital in Denmark, and 9 UK hyperbaric medicine facilities
Participants	**Criteria for defining the condition being treated:** people who required dental extractions or implant placement in the mandible with prior RT > 50 Gy **Inclusion criteria (not listed above):** men and women aged > 18 years with an indication for mandible surgery **Exclusion criteria (not listed above):** none reported **Baseline characteristics** **Overall cohort** Number of participants at enrolment: 144 Number randomised: 144 participants Number included in analyses: 100 participants Age: mean 58.2 (SD 10.1) years Sex: men 28 (28%), women 72 (72%) Treatment history: RT dose: 62.9 (SD 9.1) Gy, RT duration: 6.2 (SD 1.7) weeks **Group 1: HBOT** Number of participants at enrolment: 72 Number randomised: 72, 14 withdrew before HBO, 3 withdrew during/after HBO or surgery, 6 withdrew after surgery, 1 lost to follow-up, 1 ineligible Number included in analyses: 47 (including 4 withdrawals following final analysis) Age: mean 58.3 (SD 10) years Sex: men 14 (30%), women 37 (70%) Treatment history: RT dose: mean 62.8 (SD 7.8) Gy, RT duration: 6.1 (SD 1.6) weeks **Group 2: control** Number of participants at enrolment: 72 Number randomised: 72; 6 withdrew before surgery, 10 withdrew after surgery, 2 lost to follow-up, 1 ineligible

Shaw 2019 *(Continued)*

	Number included in analyses: 53; 3 withdrew following final analysis but included Age: mean 58.2 (SD 10.4) years Sex: men 14 (27%), women 29 (73%) Treatment history: RT dose: mean 63 (SD 10.2) Gy, RT duration: 6.2 (SD 1.7) weeks **Pretreatment group differences:** differences in dropout rate; baseline characteristics were similar whether comparison was made as per protocol or for the primary endpoint.
Interventions	**HBOT:** 100% oxygen 2.4 ATA, 30 daily dives for 80–90 minutes 20 immediately before and 10 after surgery **Control:** no hyperbaric treatment **Co-interventions:** chlorhexidine mouthwash 10 mL for 1 minute and 3 times a day rinse for 5 days and antibiotics amoxicillin 3 g 1 hour preoperatively or 1 g intravenously and 250 mg 3 times a day postoperatively
Outcomes	**Outcomes included in the review** **Outcome 1: diagnosis of ORN at 6 months** Incidence of ORN: HBOT: 3/47 (6.4%), control: 3/53 (5.7%); odds ratio 1.13, 95% CI 0.14 to 8.92; P = 1. **Outcome 2: grade of ORN** At 6 months: Notani Grade 1 for 2 participants, Grade 2 for 1 participant and grade 3 for 3 participants **Outcome 3: ORN at other time points** 3 months: HBOT: 3/45 (7%), control group: 4/55 (7%); odds ratio 0.91, 95% CI 0.13 to 5.72; P > 0.99 12 months: no new cases between 6 and 12 months and no healing; same measure as 6 months **Outcome 4: acute symptoms within first 7 days of surgery** Pain: HBOT: 11.53 (SD 5.55), 42 participants; standard: 13.79 (SD 5.69), 37 participants Swelling: HBOT: 9.97 (SD 3.79), 41 participants; standard: 12.36 (SD 4.74), 37 participants Bleeding: HBOT: 7.03 (SD 1.79), 41 participants; standard: 8.54 (SD 3.28), 37 participants Mouth opening: HBOT: 8.44 (SD 3.51), 40 participants; standard: 13.43 (SD 6.79), 37 participants Eating: HBOT: 13.18 (SD 7.49), 40 participants; standard: 20.42 (SD 8.14); 33 participants HBOT group had less pain (P = 0.0458), swelling (P = 0.0182), bleeding (P = 0.0375), mouth opening problems (P = 0.004) and eating (P = 0.004). Higher proportion were comfortable at day 8: odds ratio 2.79, CI 1.01 to 8.05; P = 0.038 **Outcome 5: pain – VAS** Baseline: HBOT: mean 0.164 (SD 0.213), median 0.063, 67 participants; standard: mean 0.232 (SD 0.289), median 0.074, 69 participants; MD −0.075, 95% CI −0.15 to 0.0001; P = 0.046 3 months: HBOT: mean 0.115 (SD 0.199), median 0.02, 46 participants; standard: mean 0.18 (SD 0.232), median 0.04, 55 participants; MD −0.057, 95% CI −0.115 to 0; P = 0.049 6 months: HBOT: mean 0.116 (SD 0.206), median 0.02, 51 participants; standard: mean 0.153 (SD 0.232), median 0.03, 54 participants; MD −0.06, 95% CI −0.121 to 0; P = 0.049 12 months: HBOT: mean 0.111 (SD 0.179), median 0.021, 44 participants; standard: mean 0.252 (SD 0.299), median 0.101, 48 participants; MD −0.076, 95% CI −0.151 to −0.001; P = 0.048

Shaw 2019 *(Continued)*

	Outcome 6: QoL Only graph provided, no actual data points
Notes	Committee recommended closing the trial after 100 evaluable participants due to the rate of ORN being much less than assumed. Outcomes that could not be extracted (and reason, e.g. no measure of variance reported for a continuous outcome).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients who meet eligibility criteria and have given informed consent were randomly assigned by the Cancer Research UK Liverpool Cancer Trials Unit (LCTU). Randomisation will be in a 1:1 ration between HBO arm and control (non-HBO) arm, stratified by recruiting centre. The randomisation code list will be generated by the LCTU trial statistician by means of block randomisation with randomly varying block length. The clinical team will be informed of the allocation of each patient by fax. Allocation of treatment was unblinded to local investigators and patients.
Allocation concealment (selection bias)	Low risk	Allocation was stratified by recruiting centre. The randomisation code list will be generated by the LCTU trial statistician by means of block randomisation with randomly varying block length. The clinical team will be informed of the allocation of each patient by fax.
Blinding (performance bias and detection bias) All outcomes	High risk	Allocation of treatment was unblinded to site investigators and participants.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded to assessment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded central review of clinical photographs and radiographs to determine ORN using the modified Notani score.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Most outcome data provided, low attrition rate and some data still able to be used despite patients withdrawing from study. 144 randomised, and 100 in final analysis.
Selective reporting (reporting bias)	Low risk	A protocol was published beforehand and all expected data were reported.
Other bias	Low risk	No other risks noted for other bias and no noted conflict of interests.

Sidik 2007

Study characteristics

Methods	**Study design:** unblinded RCT designed to evaluate the effect of HBOT on QoL after pelvic irradiation

Sidik 2007 *(Continued)*

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 was 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. Quote: "The block randomisation was performed."
Allocation concealment (selection bias)	Unclear risk	No information.
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 made assessment difficult.

Svalestad 2014

Study characteristics	
Methods	**Study design:** 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
Interventions	**HBOT:** 100% oxygen at 2.5 ATA for 90 minutes daily for 20–40 (mean 29) sessions over 6 weeks **Control**

Svalestad 2014 *(Continued)*

Outcomes	Laser Doppler flowmetry, transcutaneous oximetry, microvascular density and vessel area
Notes	2 participants refused tissue biopsies so did not contribute data to tissue microvascular measures.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Group assignment was made after enrolment using a predetermined randomized allocation sequence."
Allocation concealment (selection bias)	Low risk	Quote: "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)	Low risk	No trial registration indicated.
Other bias	Low risk	No other source of bias detected.

Teguh 2009

Study characteristics	
Methods	**Study design:** unblinded RCT
Participants	19 people with a diagnosis of nasopharyngeal or oropharyngeal carcinoma and treated with RT (47–70 Gy) with or without chemotherapy. HBOT given 2 days after completion of RT/chemotherapy HBOT group 6 male, 2 female Control group 6 male, 5 female
Interventions	**HBOT:** 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. Quote: "Patients were randomized by the trial office … by use of a block of several randomized sizes. Patients were stratified by tumour 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	Quote: "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.

ADL: Activities of Daily Living; ATA: atmospheres absolute; BMI: body mass index; cGy: Centi-Gray; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 Question Core Questionnaire; EORTC QLQ-H&N35: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module; EPIC: Expanded Prostate Index Composite Score; HA: hyaluronic acid; HBO: hyperbaric oxygen; HBOT: hyperbaric oxygen therapy; IBDQ: Inflammatory Bowel Disease Questionnaire; IQR: interquartile range; ITT: intention-to-treat; LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic; LRMGS: Late Radiation Morbidity Grading Scheme; ORN: osteoradionecrosis; QoL: quality of life; RCT: randomised controlled trial; RT: radiotherapy; SD: standard deviation; SF-36: 36-item Short Form; UKU-SERS: UKU Side Effect Rating Scale; VAS: Visual Analogue Scale.

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 a randomised comparison.

Study	Reason for exclusion
Denton 2002	Systematic review, no new data.
Gal 2003	Retrospective cohort study.
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.
Song 2018	Not examining late radiation tissue injury, examined keloids outcomes.
Tobey 1979	RCT but no quantitative data given. Both groups received some HBOT (1.2 ATA vs 2.0 ATA)

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

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

Batenburg 2020

Study name	Assessing the effect of hyperbaric oxygen therapy in breast cancer patients with late radiation toxicity (HONEY trial)
Methods	The HONEY trial will be conducted within the Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation (UMBRELLA). Within UMBRELLA, people with breast cancer referred for radiotherapy to the University Medical Centre Utrecht are eligible for inclusion
Participants	Participation ≥ 12 months in UMBRELLA, moderate/severe breast or chest wall pain, completed primary breast cancer treatment except hormonal treatment, no prior treatment with HBOT, no contraindications for HBOT, no clinical signs of metastatic or recurrent disease
Interventions	**HBOT:** 30–40 HBOT treatment sessions in a high pressure chamber (2.4 ATA) - inhale 100% oxygen through a mask. **Control** 120 participants randomised on 2:1 ratio
Outcomes	Physical outcomes, quality of life, fatigue, and cosmetic satisfaction at 3 months' follow-up.
Starting date	November 2019
Contact information	MCT Batenburg, Department of Radiation Oncology, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CZ Utrecht, the Netherlands
Notes	ClinicalTrials.gov. NCT04193722. Registered on 10 December 2019.

Bulsara 2019

Study name	Protocol for prospective randomised assessor-blinded pilot study comparing hyperbaric oxygen therapy with PENtoxifylline+TOcopherol±CLOdronate for the management of early osteoradionecrosis of the mandible
Methods	Recruit 16 participants who will be randomly allocated to HBOT or PENTOCLO. After a 4-week period of uniform 'pretreatment' medication, participants will commence their allocated treatment. Computer-generated block randomisation Random numbers
Participants	Participants to be stratified by grade of ORN, comorbidities, sex, age, socioeconomic status and smoking status. Inclusion criteria: diagnosed with grade 1 Notani score ORN by an Oral and Maxillofacial surgeon, ORN defined as area of exposed devitalised irradiated bone that fails to heal over 3–6 months in the absence of local neoplastic disease and > 20 mm^2 in size Exclusion criteria: spontaneously healing ORN; undergone previous treatment for ORN (PENTO, HBO or surgery); pregnant at time of therapy; received previous antiresorptive or antiangiogenic medications
Interventions	**Control (medication group):** 4 weeks of 'pretreatment' therapy to reduce inflammation, infection and pain consisting of 2 g daily of amoxicillin + clavulanic acid 875/125 mg (1 g morning and night), fluconazole 50 mg daily (morning), prednisolone 16 mg daily (morning) orally. 'Therapeutic phase' then commences immediately and consists of 5 days of pentoxifylline 800 mg (400 mg morning and night) and 1000 IU vitamin E (morning) (Monday to Friday) orally Patients that have fully healed (defined by complete mucosal coverage of the bony defect excepting minor bone spicules of < 20 mm present for ≥ 6 months and that have no ongoing pain) will continue to take the medication and be reviewed up to the 18-month follow-up point at which time they will cease. Patients that are not fully healed will also continue to take the medication and be reviewed up to the 18-month follow-up point at which time a decision will be made in conjunction with their treating consultant about whether to continue with the medication or to offer an alternative treatment. **HBOT:** 4 weeks of 'pretreatment' therapy as above. 'Therapeutic phase' incorporates HBOT prescribed for each participant based on Marx's protocol of 30 dives at 2.4 ATA for 90 minutes per dive, the treatment will be monitored and administered by specialist physicians who are not part of the trial team in a dedicated HBOT unit and will be the same for all participants in the HBOT arm.
Outcomes	Primary outcome: successful healing, improvement or worsening of ORN of the mandible (measured by 2 blinded independent complete mucosal coverage and absence of pain over involved area) Secondary outcome: complications that arise from treatment.
Starting date	January 2019
Contact information	Dr Vishal M Bulsara; vishal. bulsara@gmail.com; School of Dentistry, Oral Health Centre of Western Australia, Crawley, Western Australia, Australia; Ear, Nose and Throat Surgery, Fiona Stanley Hospital, Murdoch, Western Australia, Australia
Notes	For this pilot study, we will recruit 8 participants per treatment arm. Demonstrates the planned enrolment and randomisation. As they are not testing a hypothesis, the initial descriptive results on efficacy of the 2 treatment arms will be used to determine an adequately powered sample size for a larger clinical trial. Assessors and investigators will be blinded to the treatment that the study participants receive. Clinical photographs will be taken in a dedicated room and de-identified prior to being assessed.

NCT00087815

Study name	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
Notes	Continuing trial not confirmed

NCT02714465

Study name	Adverse radiation effects after gamma knife radio surgery and hyperbaric oxygen therapy (GKSH-BO)
Methods	Single group assignment, interventional
Participants	Participants will be recruited on the basis of the presence of cerebral radionecrosis after gamma knife surgery, documented by both clinical examination (Rankin Scale) and instrumental imaging (magnetic resonance imaging)
Interventions	HBOT
Outcomes	Evaluation of clinical improvement; evaluation of the reduction of the extent of oedema lesion documented by magnetic resonance imaging; measurement of complications from HBOT and their severity
Starting date	March 2016
Contact information	Simonetta Passarani, MD +39 02 6444 ext 4637; simonetta.passarani@ospedaleniguarda.it
Notes	Last update posted: 27 June 2018

NCT03144206

Study name	Evaluation of hyperbaric oxygen therapy on wound healing following management of soft tissue sarcoma with neo-adjuvant radiation and surgical resection
Methods	RCT
Participants	People with soft tissue sarcomas over 18 years

NCT03144206 *(Continued)*

Interventions	HBOT
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, North Carolina; william.eward@duke.edu
Notes	Last update posted: 18 October 2018

NCT03916068

Study name	Acute post-radiation hyperbaric oxygen (HBO2) for breast cancer patients who have recently completed radiation therapy
Methods	Parallel assignment, RCT
Participants	People with breast cancer
Interventions	HBOT Pentoxifylline Vitamin E supplementation
Outcomes	Change in breast fibrosis using Bakers Grade Assessment; objective measurements of tissue pliability using a Tissue Compliance Meter, participants' sense of well-being using SF-20 Quality of life survey; pain in radiated breasts using a Visual Analogue Scale; presence of delayed wound healing, surgical complications, implant revision or loss
Starting date	July 2019
Contact information	Lauren Elliott; 503-413-8199; oncologyresearch@lhs.org
Notes	NCT03916068

NCT04934644

Study name	The effect of hyperbaric oxygen treatment in patients with osteoradionecrosis
Methods	Parallel assigned non-randomised clinical trial
Participants	People with ORN
Interventions	HBOT
Outcomes	Soft and Hard Tissue Healing Index; change in stage of ORN; infection; transcutaneous perfusion measurement; perceived pain; mouth opening capacity; secretion of saliva; perceived quality of life; alkaline phosphatase
Starting date	March 2019

NCT04934644 *(Continued)*

Contact information	Louise Sameby; +46313436713; louise.sameby@vgregion.se Göran Kjeller, Docent; +46104417750; goran.kjeller@odontologi.gu.se
Notes	Estimated completion March 2024

ATA: atmospheres absolute; 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; SF-20: 20-item Short Form; RCT: randomised controlled trial.

DATA AND ANALYSES

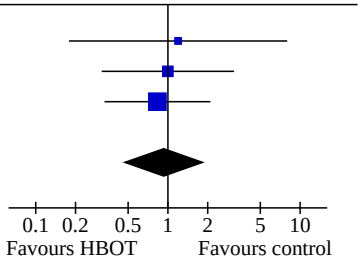
Comparison 1. Death

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death at 1 year	3	166	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.47, 1.83]

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

Study or Subgroup	HBOT Events	HBOT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2004	2	31	2	37	13.2%	1.19 [0.18 , 7.99]
Schoen 2007	4	13	4	13	28.9%	1.00 [0.32 , 3.17]
Sidik 2007	6	32	9	40	57.9%	0.83 [0.33 , 2.10]
Total (95% CI)		**76**		**90**	**100.0%**	**0.93 [0.47 , 1.83]**
Total events:	12		15			

Heterogeneity: Chi² = 0.14, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.83)
Test for subgroup differences: Not applicable



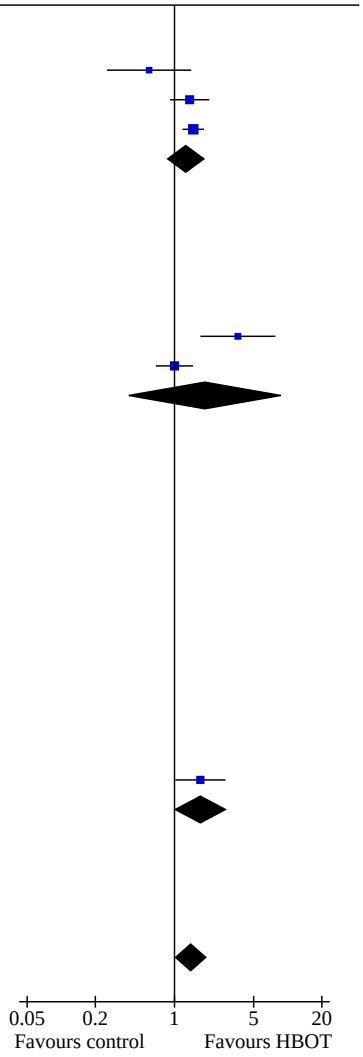
Comparison 2. Complete resolution or significant improvement of problem

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Complete or significant improvement	7	501	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.02, 1.89]
2.1.1 Osteoradionecrosis	3	239	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.87, 1.82]
2.1.2 Radiation cystitis	2	109	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.40, 8.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.3 Radiation brachioplexopathy	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.1.4 Radiation proctitis	1	120	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.02, 2.82]
2.2 Complete or significant improvement (removal of non-equivalent comparator)	6	465	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.07, 2.12]
2.2.1 Osteoradionecrosis	3	239	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.87, 1.82]
2.2.2 Radiation cystitis	1	73	Risk Ratio (M-H, Random, 95% CI)	3.63 [1.69, 7.79]
2.2.3 Radiation brachioplexopathy	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2.4 Radiation proctitis	1	120	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.02, 2.82]
2.3 Sensitivity analysis for missing data – best case	7	570	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.11, 2.60]
2.3.1 Osteoradionecrosis	3	271	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.86, 2.40]
2.3.2 Radiation cystitis	2	115	Risk Ratio (M-H, Random, 95% CI)	1.99 [0.35, 11.27]
2.3.3 Radiation brachioplexopathy	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3.4 Radiation proctitis	1	150	Risk Ratio (M-H, Random, 95% CI)	2.73 [1.66, 4.49]
2.4 Sensitivity analysis for missing data – worst case	7	570	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.66, 1.46]
2.4.1 Osteoradionecrosis	3	271	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.45, 1.76]
2.4.2 Radiation cystitis	2	115	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.58, 3.78]
2.4.3 Radiation brachioplexopathy	1	34	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.65]
2.4.4 Radiation proctitis	1	150	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.47, 0.93]

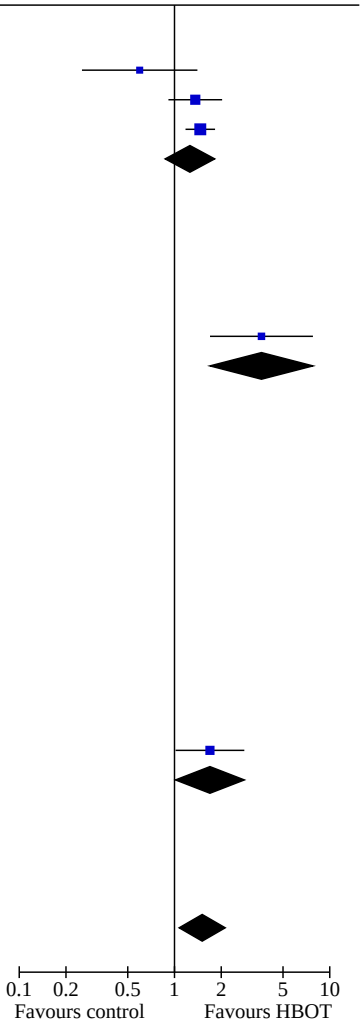
Analysis 2.1. Comparison 2: Complete resolution or significant improvement of problem, Outcome 1: Complete or significant improvement

Study or Subgroup	HBOT Events	HBOT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Osteoradionecrosis						
Annane 2004	6	31	12	37	8.9%	0.60 [0.25 , 1.40]
Forner 2022	21	30	18	35	19.4%	1.36 [0.91 , 2.03]
Marx 1999a	48	52	34	54	25.2%	1.47 [1.18 , 1.83]
Subtotal (95% CI)		**113**		**126**	**53.5%**	**1.26 [0.87 , 1.82]**
Total events:	75		64			
Heterogeneity: Tau² = 0.06; Chi² = 4.60, df = 2 (P = 0.10); I² = 57%						
Test for overall effect: Z = 1.22 (P = 0.22)						
2.1.2 Radiation cystitis						
Oscarsson 2019	25	39	6	34	10.4%	3.63 [1.69 , 7.79]
Shao 2011	15	20	12	16	20.0%	1.00 [0.68 , 1.46]
Subtotal (95% CI)		**59**		**50**	**30.4%**	**1.85 [0.40 , 8.67]**
Total events:	40		18			
Heterogeneity: Tau² = 1.15; Chi² = 13.16, df = 1 (P = 0.0003); I² = 92%						
Test for overall effect: Z = 0.78 (P = 0.43)						
2.1.3 Radiation brachioplexopathy						
Pritchard 2001	0	17	0	16		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.1.4 Radiation proctitis						
Clarke 2008	29	64	15	56	16.1%	1.69 [1.02 , 2.82]
Subtotal (95% CI)		**64**		**56**	**16.1%**	**1.69 [1.02 , 2.82]**
Total events:	29		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.02 (P = 0.04)						
Total (95% CI)		**253**		**248**	**100.0%**	**1.39 [1.02 , 1.89]**
Total events:	144		97			
Heterogeneity: Tau² = 0.08; Chi² = 14.01, df = 5 (P = 0.02); I² = 64%						
Test for overall effect: Z = 2.10 (P = 0.04)						
Test for subgroup differences: Chi² = 0.98, df = 2 (P = 0.61), I² = 0%						

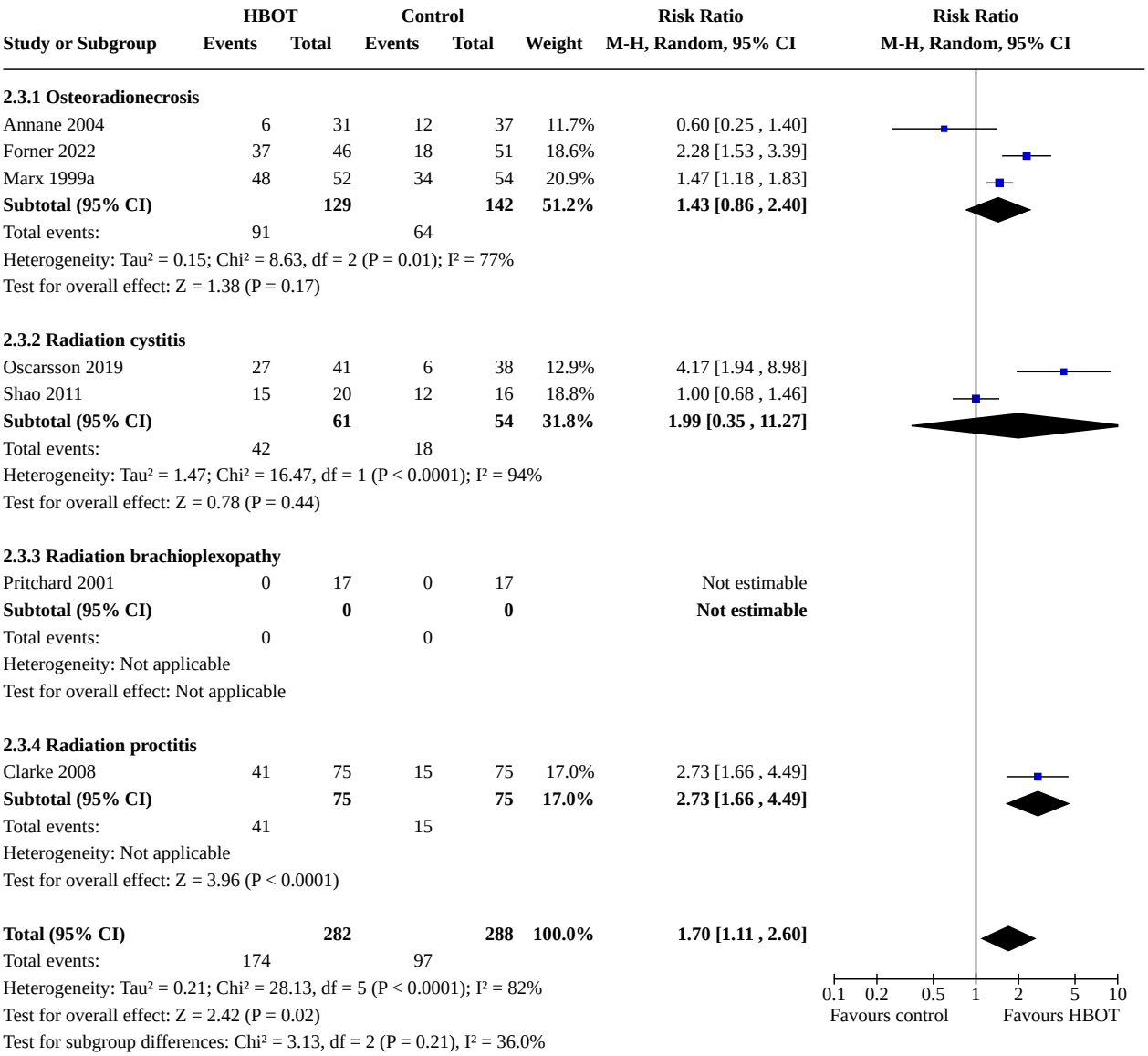


Analysis 2.2. Comparison 2: Complete resolution or significant improvement of problem, Outcome 2: Complete or significant improvement (removal of non-equivalent comparator)

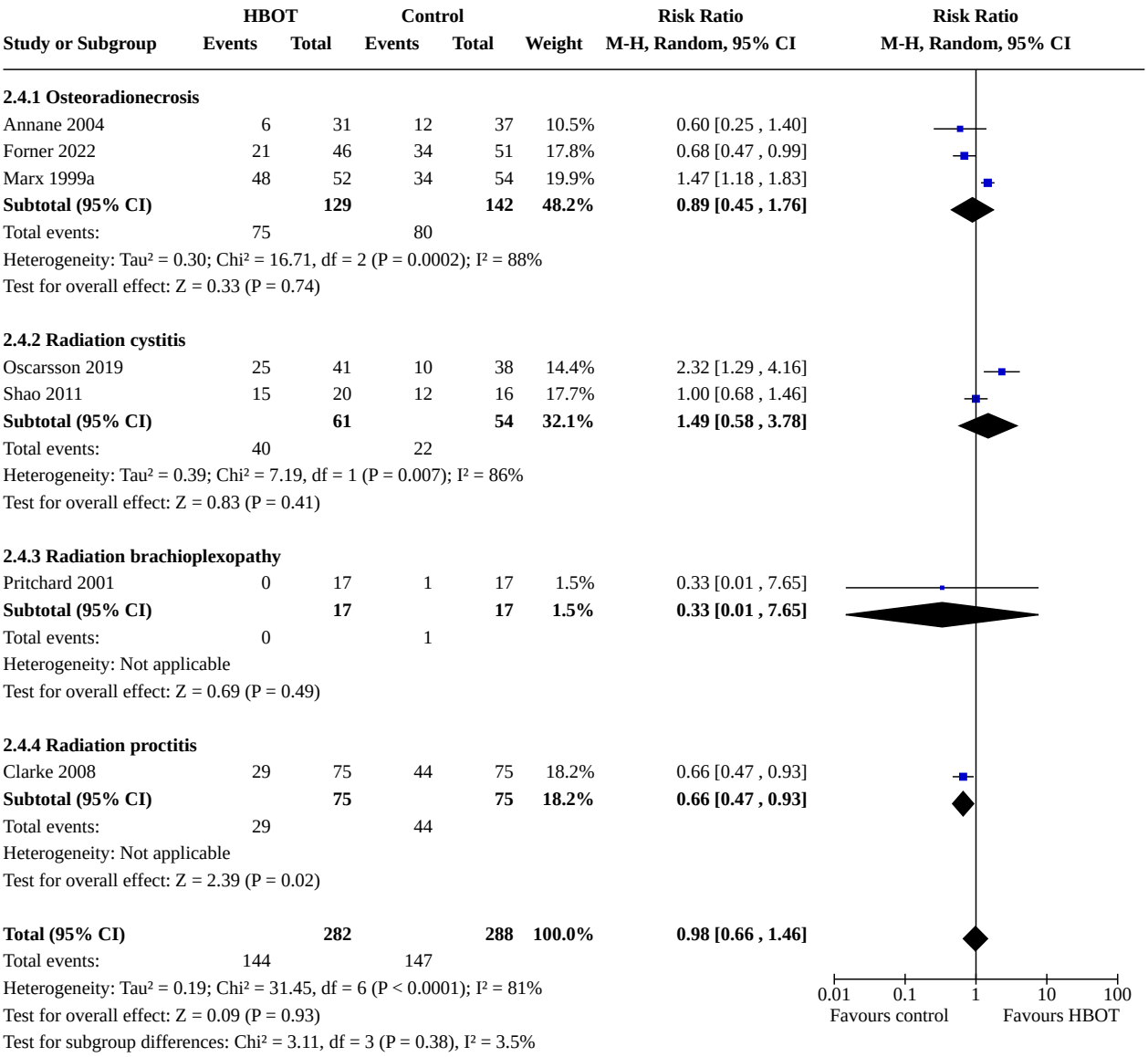
Study or Subgroup	HBOT Events	HBOT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Osteoradionecrosis						
Annane 2004	6	31	12	37	11.1%	0.60 [0.25 , 1.40]
Forner 2022	21	30	18	35	24.3%	1.36 [0.91 , 2.03]
Marx 1999a	48	52	34	54	31.6%	1.47 [1.18 , 1.83]
Subtotal (95% CI)		**113**		**126**	**67.0%**	**1.26 [0.87 , 1.82]**
Total events:	75		64			
Heterogeneity: Tau² = 0.06; Chi² = 4.60, df = 2 (P = 0.10); I² = 57%						
Test for overall effect: Z = 1.22 (P = 0.22)						
2.2.2 Radiation cystitis						
Oscarsson 2019	25	39	6	34	12.9%	3.63 [1.69 , 7.79]
Subtotal (95% CI)		**39**		**34**	**12.9%**	**3.63 [1.69 , 7.79]**
Total events:	25		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.31 (P = 0.0009)						
2.2.3 Radiation brachioplexopathy						
Pritchard 2001	0	17	0	16		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.2.4 Radiation proctitis						
Clarke 2008	29	64	15	56	20.1%	1.69 [1.02 , 2.82]
Subtotal (95% CI)		**64**		**56**	**20.1%**	**1.69 [1.02 , 2.82]**
Total events:	29		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.02 (P = 0.04)						
Total (95% CI)		**233**		**232**	**100.0%**	**1.51 [1.07 , 2.12]**
Total events:	129		85			
Heterogeneity: Tau² = 0.08; Chi² = 10.27, df = 4 (P = 0.04); I² = 61%						
Test for overall effect: Z = 2.36 (P = 0.02)						
Test for subgroup differences: Chi² = 6.13, df = 2 (P = 0.05), I² = 67.4%						



Analysis 2.3. Comparison 2: Complete resolution or significant improvement of problem, Outcome 3: Sensitivity analysis for missing data – best case



Analysis 2.4. Comparison 2: Complete resolution or significant improvement of problem, Outcome 4: Sensitivity analysis for missing data – worst case



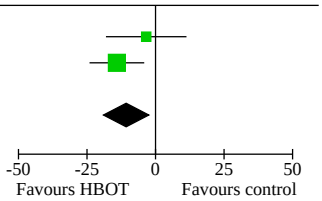
Comparison 3. Resolution of pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Pain score change at 12 months	2	157	Mean Difference (IV, Fixed, 95% CI)	-10.72 [-18.97, -2.47]

Analysis 3.1. Comparison 3: Resolution of pain, Outcome 1: Pain score change at 12 months

Study or Subgroup	HBOT Mean	HBOT SD	HBOT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Forner 2022	21.7	31.2	30	25.1	28.8	35	31.6%	-3.40 [-18.09 , 11.29]
Shaw 2019	11.1	17.9	44	25.2	29.9	48	68.4%	-14.10 [-24.08 , -4.12]
Total (95% CI)			**74**			**83**	**100.0%**	**-10.72 [-18.97 , -2.47]**

Heterogeneity: Chi² = 1.40, df = 1 (P = 0.24); I² = 28%
Test for overall effect: Z = 2.55 (P = 0.01)
Test for subgroup differences: Not applicable

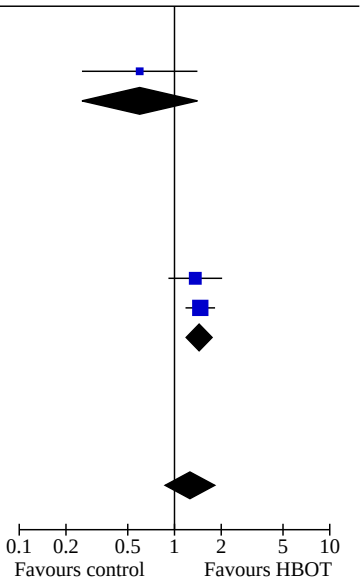


Comparison 4. Osteoradionecrosis (ORN)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Complete resolution or significant improvement	3	239	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.87, 1.82]
4.1.1 Severe ORN excluded	1	68	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.25, 1.40]
4.1.2 All grades of ORN	2	171	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.19, 1.75]

Analysis 4.1. Comparison 4: Osteoradionecrosis (ORN), Outcome 1: Complete resolution or significant improvement

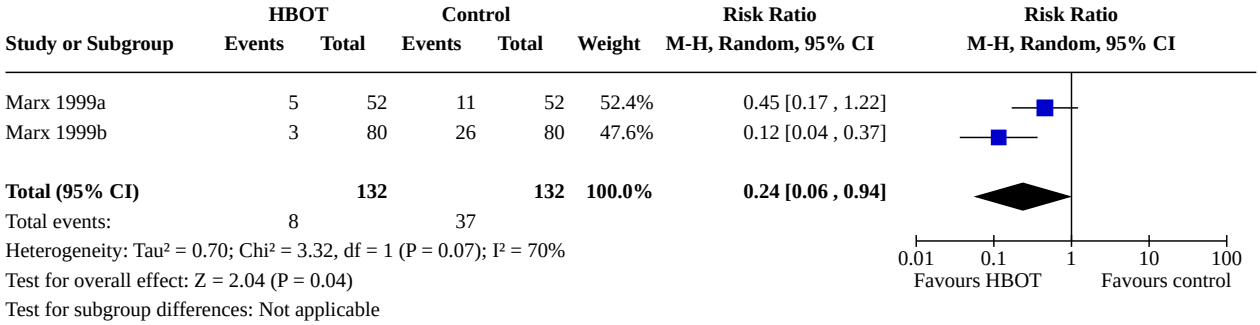
Study or Subgroup	HBOT Events	HBOT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Severe ORN excluded						
Annane 2004	6	31	12	37	14.1%	0.60 [0.25 , 1.40]
Subtotal (95% CI)		**31**		**37**	**14.1%**	**0.60 [0.25 , 1.40]**
Total events:	6		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
4.1.2 All grades of ORN						
Forner 2022	21	30	18	35	35.6%	1.36 [0.91 , 2.03]
Marx 1999a	48	52	34	54	50.3%	1.47 [1.18 , 1.83]
Subtotal (95% CI)		**82**		**89**	**85.9%**	**1.44 [1.19 , 1.75]**
Total events:	69		52			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 3.73 (P = 0.0002)						
Total (95% CI)		**113**		**126**	**100.0%**	**1.26 [0.87 , 1.82]**
Total events:	75		64			
Heterogeneity: Tau² = 0.06; Chi² = 4.60, df = 2 (P = 0.10); I² = 57%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Test for subgroup differences: Chi² = 3.88, df = 1 (P = 0.05), I² = 74.2%						



Comparison 5. Head and neck soft tissues

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Wound dehiscence	2	264	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.06, 0.94]

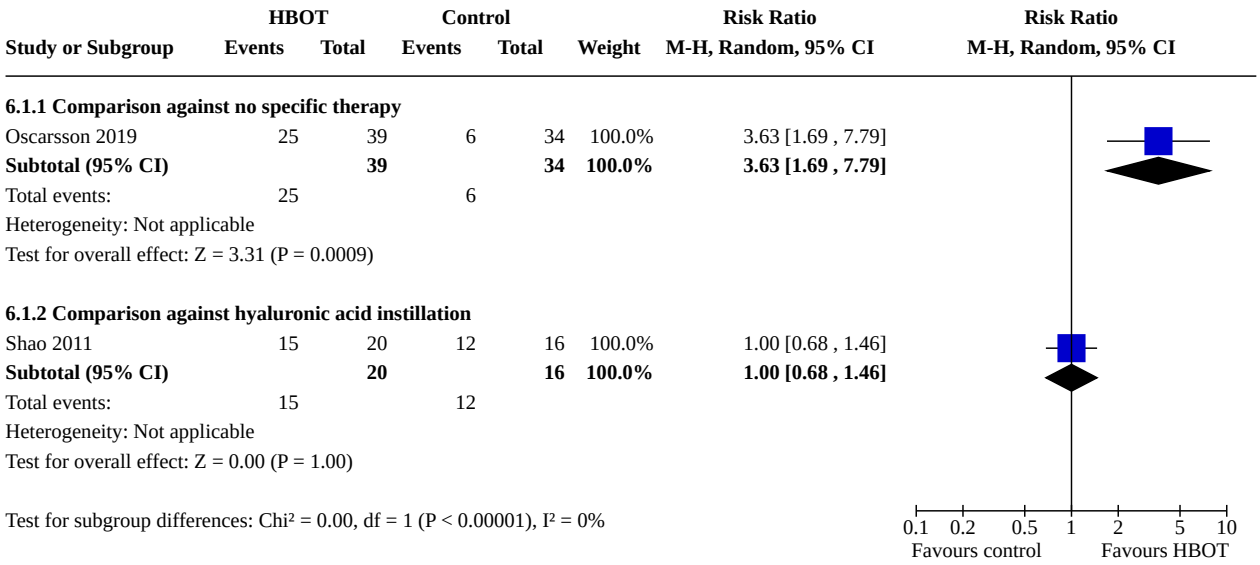
Analysis 5.1. Comparison 5: Head and neck soft tissues, Outcome 1: Wound dehiscence



Comparison 6. Radiation cystitis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Complete resolution or substantial improvement in condition	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1.1 Comparison against no specific therapy	1	73	Risk Ratio (M-H, Random, 95% CI)	3.63 [1.69, 7.79]
6.1.2 Comparison against hyaluronic acid instillation	1	36	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.68, 1.46]

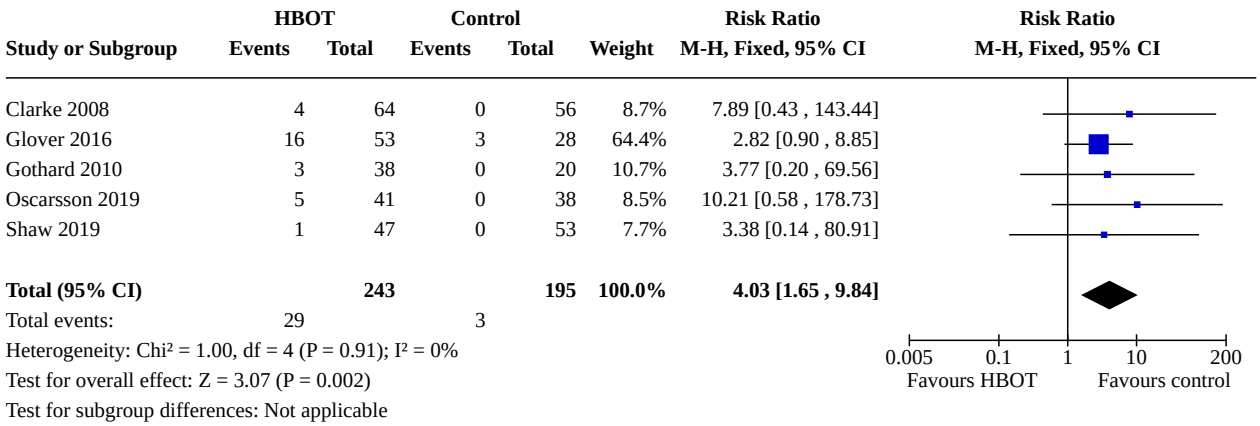
Analysis 6.1. Comparison 6: Radiation cystitis, Outcome 1: Complete resolution or substantial improvement in condition



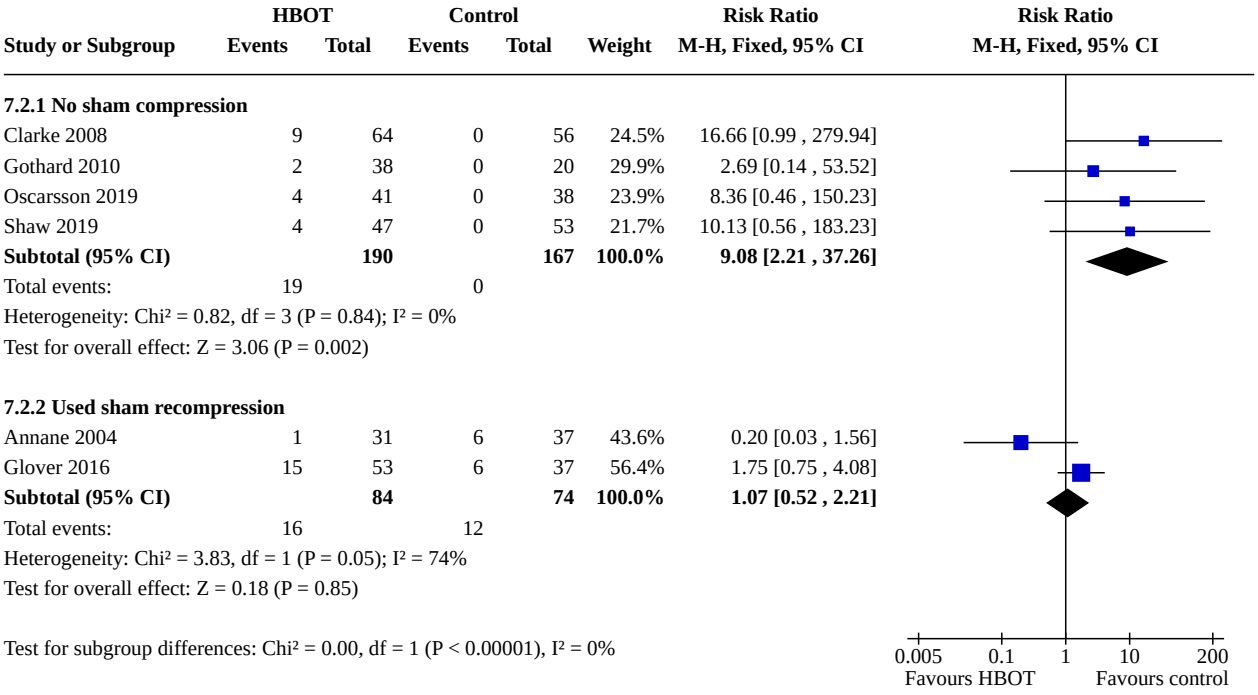
Comparison 7. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Reduction in visual acuity	5	438	Risk Ratio (M-H, Fixed, 95% CI)	4.03 [1.65, 9.84]
7.2 Ear barotrauma	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.2.1 No sham compression	4	357	Risk Ratio (M-H, Fixed, 95% CI)	9.08 [2.21, 37.26]
7.2.2 Used sham recompression	2	158	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.52, 2.21]

Analysis 7.1. Comparison 7: Adverse events, Outcome 1: Reduction in visual acuity



Analysis 7.2. Comparison 7: Adverse events, Outcome 2: Ear barotrauma



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

Appendix 6. Study data extraction form

Data extraction form (Excel)

Study				
Reference/s				
Eligibility for inclusion in review				
	Randomisation?……..	yes	no	unknown
		comment		
	Allocation blind?……	yes	no	unknown
		comment		
	Intervention blind?……	yes	no	unknown
		comment		
	complete follow-up?……	yes	no	unknown
		comment		
	Outcome assessment blind? ……	yes	no	unknown
		comment		
Participants	Characteristics of patient population			
	Exclusions……..			
Flow diagram	Number eligible……	……....	…….	

(Continued)

	Excluded pre-randomisation……	……				
	Numbers randomised……	……	……..			
			experi-mental		control	
	Excluded post-randomisation……	……				
	Number analysed……	……				
Intervention	Experimental……..					
	Control……					
			Number assessed	Number with outcome	Blinded assessment	Number assessed	Number with outcome
Dichotomous outcomes			N	n		N	n
Primary outcome							

(Continued)

	Death	Y / N / ?
	Problem resolution	Y / N / ?
	Improved LENT-SOMA	Y / N / ?
	ORN - mucosal cover achieved	Y / N / ?
	ORN - bony continuity established	Y / N / ?
	Need for surgery	Y / N / ?
	Sinus tract healed	Y / N / ?
	Head and neck - wound dehisced	Y / N / ?
	Head and neck - laryngectomy	Y / N / ?
	Head and neck - major vessel haem.	Y / N / ?
	Bladder/bowel - bleeding stopped	Y / N / ?
	Bladder/bowel - major op needed	Y / N / ?
	Neuro - improved motor ability	Y / N / ?
	Neuro - improved V/A	Y / N / ?
secondary outcomes		
	Pain resolved/improved	Y / N / ?
	Oedema resolved/improved	Y / N / ?
	Improvement in QOL	Y / N / ?
	Radiology or MRI improved	Y / N / ?
	Head and neck - reversal of trache	Y / N / ?
	Cystoscopic improvement	Y / N / ?

(Continued)

	Frequency improved				Y / N / ?			
	Dysuria improved				Y / N / ?			
	Steroid dose down							
	Neuro - improved AODL							
	Neuro - improved sensation							
Continuous variables		Number assessed				Number assessed		
		N	Mean	SD		N	Mean	SD
Primary outcome								
	LENT-SOMA scale				Y / N / ?			
	Blood loss							
secondary outcomes								
	Pain score				Y / N / ?			
	QOL assessment				Y / N / ?			
	ORN - radi				Y / N / ?			
	Rate of healing				Y / N / ?			
	Frequency improved				Y / N / ?			
	AODL				Y / N / ?			
	Steroid dose				Y / N / ?			
					Y / N / ?			

(Continued)

Notes

WHAT'S NEW

Date	Event	Description
15 August 2023	New search has been performed	Four new studies included
15 August 2023	New citation required and conclusions have changed	Search updated 24 January 2022

HISTORY

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

Date	Event	Description
9 March 2016	New search has been performed	The review has been updated. Specifically we have: 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.
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.
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

ZCL: principal author, search strategy and execution, data extraction, critical appraisal and analysis

MB: conception, principal author mentor, search strategy and execution, hyperbaric medicine content expert, methodology

GCH: searches, critical appraisal, data extraction, hyperbaric medicine content expert

CPA: search strategy and execution, data extraction, hyperbaric medicine content expert

JF: radiation oncology and hyperbaric medicine content expert

RS: editorial advice, radiation oncology content expert

CM: background, radiation oncology content expert.

DECLARATIONS OF INTEREST

ZCL: none. ZCL is a trainee in diving, hyperbaric and emergency medicine.

MB: none. MB is a hyperbaric physician who regularly treats people with LRTI.

GCH: none. GCH is a hyperbaric physician who regularly treats people with LRTI.

CPA: none. CPA is a hyperbaric physician who regularly treats people with LRTI.

JF: none. JF has previous hyperbaric experience and is a radiation oncologist who refers people with LRTI for HBOT.

RS: none. RS is a radiation oncologist who refers people with LRTI for HBOT.

CM: none. CM is a radiation oncologist who refers people with LRTI for HBOT.

SOURCES OF SUPPORT

Internal sources

- No source of support, Other

  No source of support

External sources

- NIHR, UK

  NIHR Cochrane infrastrucure funding to the Gynaecologial, Neuro-oncology and Orphan Cancer Group

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)

*Barotrauma [therapy]; Disease Progression; *Hyperbaric Oxygenation [methods]; *Neoplasms [therapy]; *Osteoradionecrosis [prevention & control]; Pain; *Radiation Injuries [prevention & control]

MeSH check words

Humans