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Hyperbaric oxygenation for tumour sensitisation to radiotherapy (Review)

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Hyperbaric oxygenation for tumour sensitisation to radiotherapy.
Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD005007.
DOI: 10.1002/14651858.CD005007.pub4.

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[Intervention Review]

Hyperbaric oxygenation for tumour sensitisation to radiotherapy

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Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 7, 2018.

Citation: Bennett MH, Feldmeier J, Smee R, Milross C. Hyperbaric oxygenation for tumour sensitisation to radiotherapy. *Cochrane Database of Systematic Reviews* 2018, Issue 4. Art. No.: CD005007. DOI: 10.1002/14651858.CD005007.pub4.

ABSTRACT

Background

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

Objectives

To assess the benefits and harms of administering radiotherapy for the treatment of malignant tumours while breathing HBO.

Search methods

In September 2017 we searched the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library Issue 8, 2017, MEDLINE, Embase, and the Database of Randomised Trials in Hyperbaric Medicine using the same strategies used in 2011 and 2015, and examined the reference lists of included articles.

Selection criteria

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

Data collection and analysis

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

Main results

We included 19 trials in this review (2286 participants: 1103 allocated to HBOT and 1153 to control).

For head and neck cancer, there was an overall reduction in the risk of dying at both one year and five years after therapy (risk ratio (RR) 0.83, 95% confidence interval (CI) 0.70 to 0.98, number needed to treat for an additional beneficial outcome (NNTB) = 11 and RR 0.82, 95% CI 0.69 to 0.98, high-quality evidence), and some evidence of improved local tumour control immediately following irradiation (RR with HBOT 0.58, 95% CI 0.39 to 0.85, moderate-quality evidence due to imprecision). There was a lower incidence of local recurrence of tumour when using HBOT at both one and five years (RR at one year 0.66, 95% CI 0.56 to 0.78, high-quality evidence; RR at five years 0.77, 95% CI 0.62 to 0.95, moderate-quality evidence due to inconsistency between trials). There was also some evidence with regard to the chance of metastasis at five years (RR with HBOT 0.45 95% CI 0.09 to 2.30, single trial moderate quality evidence imprecision). No trials reported a quality of life assessment. Any benefits come at the cost of an increased risk of severe local radiation reactions with HBOT (severe radiation

reaction RR 2.64, 95% CI 1.65 to 4.23, high-quality evidence). However, the available evidence failed to clearly demonstrate an increased risk of seizures from acute oxygen toxicity (RR 4.3, 95% CI 0.47 to 39.6, moderate-quality evidence).

For carcinoma of the uterine cervix, there was no clear benefit in terms of mortality at either one year or five years (RR with HBOT at one year 0.88, 95% CI 0.69 to 1.11, high-quality evidence; RR at five years 0.95, 95% CI 0.80 to 1.14, moderate-quality evidence due to inconsistency between trials). Similarly, there was no clear evidence of a benefit of HBOT in the reported rate of local recurrence (RR with HBOT at one year 0.82, 95% CI 0.63 to 1.06, high-quality evidence; RR at five years 0.85, 95% CI 0.65 to 1.13, moderate-quality evidence due to inconsistency between trials). We also found no clear evidence for any effect of HBOT on the rate of development of metastases at both two years and five years (two years RR with HBOT 1.05, 95% CI 0.84 to 1.31, high quality evidence; five years RR 0.79, 95% CI 0.50 to 1.26, moderate-quality evidence due to inconsistency). There were, however, increased adverse effects with HBOT. The risk of a severe radiation injury at the time of treatment with HBOT was 2.05, 95% CI 1.22 to 3.46, high-quality evidence. No trials reported any failure of local tumour control, quality of life assessments, or the risk of seizures during treatment.

With regard to the treatment of urinary bladder cancer, there was no clear evidence of a benefit in terms of mortality from HBOT at one year (RR 0.97, 95% CI 0.74 to 1.27, high-quality evidence), nor any benefit in the risk of developing metastases at two years (RR 2.0, 95% CI 0.58 to 6.91, moderate-quality evidence due to imprecision). No trial reported on failure of local control, local recurrence, quality of life, or adverse effects.

When all cancer types were combined, there was evidence for an increased risk of severe radiation tissue injury during the course of radiotherapy with HBOT (RR 2.35, 95% CI 1.66 to 3.33, high-quality evidence) and of oxygen toxic seizures during treatment (RR with HBOT 6.76, 96% CI 1.16 to 39.31, moderate-quality evidence due to imprecision).

Authors' conclusions

We found evidence that HBOT improves local tumour control, mortality, and local tumour recurrence for cancers of the head and neck. These benefits may only occur with unusual fractionation schemes. Hyperbaric oxygenation therapy is associated with severe tissue radiation injury. Given the methodological and reporting inadequacies of the included studies, our results demand a cautious interpretation. More research is needed for head and neck cancer, but is probably not justified for uterine cervical or bladder cancer. There is little evidence available concerning malignancies at other anatomical sites.

PLAIN LANGUAGE SUMMARY

High-pressure oxygen breathing during radiotherapy for cancer treatment

Review question
For people with solid cancers, we asked if the combination of radiotherapy and hyperbaric oxygen (HBO) breathing could reduce mortality and the chance of cancer spread when compared to radiotherapy alone or to radiotherapy and an alternative approach to reducing mortality and cancer spread.

Background
Invasive cancer is a major health problem and results in the death of millions of people each year. Many solid cancers are low in oxygen (hypoxic), which means they are resistant to the effect of radiotherapy treatment. For this reason, it has been suggested that raising the oxygen levels in the tumours by administering HBO breathing could make treatment with radiotherapy more effective.

Study characteristics
We found 19 randomised trials that together included 2286 participants. The dose of oxygen per treatment session in the HBO arm was remarkably uniform, with all trials except one administering external beam radiation therapy at 3 atmospheres absolute (ATA). However, the number of treatments given ranged widely, from two sessions only, separated by three weeks, up to 40 sessions over eight weeks.The total dose of radiation was generally reduced in the HBO participants in order to reduce side effects. The follow-up period varied between trials, from six months to 10 years, although most studies followed participants for between two and five years.

Key results
Adding HBO to the treatment of head and neck cancers reduced mortality at both one year and five years after therapy. Local tumour recurrence was also less likely with HBO at one year and five years in head and neck cancer. However, these advantages are achieved at the cost of some adverse effects. There was a significant increase in the rate of severe radiation tissue injury and the chance of seizures during HBO therapy.

Quality of the evidence
The quality of evidence was generally high with close agreement between several different trials. Similarly, there was high-quality evidence of an increased risk of having a severe reaction to the radiation while breathing HBO. The evidence for an increased risk of seizures during treatment when using HBO was of moderate quality, mainly because of the small numbers of seizures seen in the included studies.

Conclusions

There is some evidence that breathing oxygen while at raised pressure may improve mortality and reduce tumour regrowth in cancers of the head and neck, but at the cost of increased side effects.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Hyperbaric oxygen versus air breathing to enhance the effectiveness of radiotherapy for tumours of the head and neck

Hyperbaric oxygen versus air breathing to enhance the effectiveness of radiotherapy for tumours of the head and neck

Patient or population: People undergoing radiation therapy for head and neck cancer
Setting: Hospital radiotherapy facility
Intervention: Hyperbaric oxygen
Comparison: Air breathing

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with air breathing	Risk with hyperbaric oxygen				
Mortality	Follow-up: 1 year	Study population		RR 0.83 (0.70 to 0.98)	710 (9 RCTs)	⊕⊕⊕⊕ HIGH	
		461 per 1000	383 per 1000 (323 to 452)				
	Follow-up: 5 years	Study population		RR 0.82 (0.69 to 0.98)	550 (6 RCTs)	⊕⊕⊕⊕ HIGH	
		486 per 1000	399 per 1000 (336 to 477)				
Failure of local tumour control (local control) Follow-up: 3 months		Study population		RR 0.58 (0.39 to 0.85)	446 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
		406 per 1000	235 per 1000 (158 to 345)				
Local recurrence (recurrence)	Local recurrence (recurrence) Follow-up: 1 year	Study population		RR 0.66 (0.56 to 0.78)	582 (5 RCTs)	⊕⊕⊕⊕ HIGH	
		627 per 1000	414 per 1000 (351 to 489)				
	Local recurrence (recurrence) Follow-up: 5 years	Study population		RR 0.77 (0.62 to 0.98)	495 (5 RCTs)	⊕⊕⊕⊖ MODERATE [2]	
		665 per 1000	512 per 1000 (1000 to 1000)				
Metastasis	Five years - head and neck	167 per 1000	75 per 1000	RR 0.45	50	⊕⊕⊕⊖ MODERATE [3]	Single trial data

			(15 to 383)	(0.09 to 2.30)	(1 RCT)	
Quality of life - not reported	-	-	-	-	-	-
Adverse effects	Severe radiation injury (severe reaction) Follow-up: 3 months	Study population		RR 2.64 (1.65 to 4.23)	323 (4 RCTs)	⊕⊕⊕⊖ MODERATE [3]
		115 per 1000	304 per 1000 (190 to 487)			
	Acute central nervous system toxicity (seizure) Follow-up: 6 weeks	Study population		RR 4.30 (0.47 to 39.60)	267 (2 RCTs)	⊕⊕⊕⊖ MODERATE [3]
		0 per 1000	0 per 1000 (0 to 0)			

*__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; **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.

[1]Downgraded one level for imprecision because sensitivity analysis for missing data marginally affected result.
[2]Downgraded one level due to inconsistency.
[3]Downgraded one level due to imprecision.

Summary of findings 2. Hyperbaric oxygen compared to air breathing for enhancing the effect of radiation for cancer of the uterine cervix

Hyperbaric oxygen compared to air breathing for enhancing the effect of radiation for cancer of the uterine cervix

Patient or population: People undergoing radiotherapy for uterine cervical cancer
Setting: Hospital radiotherapy facilities
Intervention: Hyperbaric oxygen
Comparison: Air breathing

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

		Risk with air breathing	Risk with hyperbaric oxygen			
Mortality	Follow-up: 1 year	Study population		RR 0.88 (0.69 to 1.11)	728 (4 RCTs)	⊕⊕⊕⊕ HIGH
		295 per 1000	260 per 1000 (204 to 327)			
	Follow-up: 5 years	Study population		RR 0.95 (0.80 to 1.14)	772 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1]
		659 per 1000	626 per 1000 (527 to 752)			
Failure of local tumour control - not reported		-	-	-	-	-
Local recurrence (recurrence)	Follow-up: 1 year	Study population		RR 0.82 (0.63 to 1.06)	714 (3 RCTs)	⊕⊕⊕⊕ HIGH
		311 per 1000	255 per 1000 (196 to 330)			
	Follow-up: 5 years	Study population		RR 0.85 (0.65 to 1.13)	772 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1]
		501 per 1000	426 per 1000 (326 to 566)			
Metastasis	Follow-up: 2 years	Study population		RR 1.05 (0.84 to 1.31)	520 (3 RCTs)	⊕⊕⊕⊕ HIGH
		347 per 1000	364 per 1000 (291 to 364)			
	Follow-up: 5 years	443 per 1000	350 per 1000 (221 to 558)	RR 0.79 (0.50 to 1.26)	456 (3 RCTs)	⊕⊕⊕⊖ MODERATE [1]
Quality of life - not reported		-	-	-	-	-
Adverse effects	Severe radiation injury (severe reaction) Follow-up: 3 months	Study population		RR 2.05 (1.22 to 3.46)	456 (3 RCTs)	⊕⊕⊕⊕ HIGH
		115 per 1000	236 per 1000 (140 to 398)			
	Acute central nervous system toxicity - not reported	-	-	-	-	-

*__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; **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.

[1] Downgradedone level due to inconsistency.

Summary of findings 3. Hyperbaric oxygen compared to air breathing for enhancing the effect of radiotherapy for a mixed group of cancers (urinary bladder, lung, rectum, oesophagus, brain)

Hyperbaric oxygen compared to air breathing for enhancing the effect of radiotherapy for a mixed group of cancers (urinary bladder, lung, rectum, oesophagus, brain)

Patient or population: People with any one of a mixed group of cancers
Setting: Hospital radiotherapy facilities
Intervention: Hyperbaric oxygen
Comparison: Air breathing

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with air breathing	Risk with hyperbaric oxygen				
Mortality with urinary bladder cancer Follow-up: 1 year	Study population		RR 0.97 (0.74 to 1.27)	330 (4 RCTs)	⊕⊕⊕⊕ HIGH	
	394 per 1000	382 per 1000 (292 to 500)				
Failure of local tumour control - not reported	-	-	-	-	-	
Local recurrence - not reported	-	-	-	-	-	
Metastases with urinary bladder cancer Follow-up: 2 years	Study population		RR 2.00 (0.58 to 6.91)	80 (2 RCTs)	⊕⊕⊕⊖ MODERATE[1]	
	73 per 1000	146 per 1000				

			(42 to 506)				
Quality of life - not reported		-	-	-	-	-	
Adverse effects	Severe radiation injury (severe reaction) Follow-up: 3 months	Study population		RR 2.35 (1.66 to 3.33)	779 (7 RCTs)	⊕⊕⊕⊕ HIGH	All cancer types included in this analysis.
		95 per 1000	223 per 1000 (158 to 316)				
	Acute neurological toxicity (seizure) Follow-up: 3 months	Study population		RR 6.76 (1.16 to 39.31)	331 (4 RCTs)	⊕⊕⊕⊖ MODERATE[1]	
		0 per 1000	47 per 1000 (9 to 122)				

*__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; __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.

1 Downgraded one level due to imprecision

BACKGROUND

Description of the condition

Invasive cancer continues to be a major world health problem. Approximately 14 million people were diagnosed with cancer in 2012 (Ferlay 2013), and it is estimated there will be 15 million new cases every year by 2020. Cancer caused 8.8 million deaths in 2015, or 17% of deaths worldwide (WHO 2017), and is the second leading cause of death in the USA, being associated with a projected 0.6 million deaths in 2017 (Seigel 2017). Radiotherapy is a well-established treatment of suitable malignancies in a wide variety of anatomical areas. In the USA, approximately 1.7 million new cases are diagnosed annually, and about 50% of these will be treated with radiation (Jemal 2002).

Description of the intervention

Hyperbaric oxygen therapy is relatively widely available in North America (where there are more than 800 facilities registered with the Undersea and Hyperbaric Medical Society), Russia, China, and Cuba, but is less well established in Europe and Australasia (UHMS 2017). Treatment involves placing the patient in a compression chamber, increasing the environmental pressure within the chamber, and administering 100% oxygen for respiration. In this way, it is possible to deliver a greatly increased pressure of oxygen to the tissues. Treatments for tumour oxygen sensitisation typically involve pressurisation to between 2.0 and 4.0 atmospheres absolute (ATA) for periods of between 20 and 30 minutes for pre-oxygenation, following which the radiation therapy is delivered while the patient continues to breathe oxygen at pressure. A range of radiation fractionation and dosing schemes has been suggested.

How the intervention might work

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

One attractive method for increasing oxygen pressure in hypoxic areas is the administration of 100% oxygen at greater than one atmosphere total pressure, a procedure known as hyperbaric oxygenation (HBO). Hyperbaric oxygenation was first used for this purpose in the 1960s and was reported by Churchill-Davidson (Churchill 1968). The technique of administering radiation whilst confined in a hyperbaric chamber was adopted in a number of centres around the world, but inherent difficulties with the physical requirements and the advent of orally administered agents to improve tumour sensitivity to radiation led to the abandonment of this combined approach during the 1980s.

Why it is important to do this review

The decisions described above were made despite the publication of a number of promising clinical trials with HBO, and it has been suggested that hyperbaric oxygenation therapy (HBOT) was abandoned before a measured evaluation could be made of its true clinical impact (Overgaard 1996). While many of the trials using HBO were included in the Overgaard 1996 review, we believe a structured systematic search may reveal further evidence, and we are aware of at least two randomised trials published after 1996 (Dische 1999; Haffty 1999).

Hyperbaric oxygenation therapy is associated with some risk of adverse effects including damage to the ears, sinuses, and lungs from the effects of pressure, temporary worsening of myopia, claustrophobia, and oxygen poisoning. Although serious adverse events are rare, HBO cannot be regarded as an entirely benign intervention. It has further been suggested that HBOT may increase the incidence and/or rate of growth of local recurrence or remote metastatic disease in people with a history of malignancy, although a comprehensive review failed to support these concerns (Feldmeier 2003). For all of these reasons, we believed a review could clarify the true value, if any, of HBOT in this area.

OBJECTIVES

To assess the benefits and harms of administering radiotherapy for the treatment of malignant tumours while breathing HBO.

1. Does the addition of HBO to radiation therapy:
   a. reduce mortality at any time following therapy?
   b. increase local tumour response?
   c. reduce the incidence of local recurrence?
   d. reduce the incidence of metastatic spread?
   e. improve the quality of life for these people?
2. Does sensitisation to radiation therapy with HBO produce any of the benefits above when compared to other agents?
3. Is HBO administration safe in this setting?

METHODS

Criteria for considering studies for this review

Types of studies

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

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

Types of participants

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

Types of interventions

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

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

Types of outcome measures

Primary outcomes

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

Secondary outcomes

1. Local recurrence at any time
2. Metastatic disease at any time
3. Quality of life assessment

Adverse effects of HBOT

Specific to combined HBOT/radiation therapy

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

General relating to HBO

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

We would report and discuss any other recorded adverse effects.

Search methods for identification of studies

Electronic searches

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

We searched the following (from inception) in November 2004 and then repeated the searches in September 2008, March 2011, and September 2017: For this review update we searched: Cochrane Central Register of Controlled Trials (CENTRAL) the Cochrane Library Issue 8 2017, MEDLINE (March 2011 to August week 5 2017), Embase (March 2011 to 2017 week 36), and an additional database developed in our hyperbaric facility (the Database of Randomised Trials in Hyperbaric Medicine, Bennett 2017) on 05/09/2017. We searched CINAHL (Cumulative Index to Nursing and Allied Health Literature) in 2004 and 2008, but not 2011 or 2017. The search strategy was broad; the strategies used are presented in Appendix 1, Appendix 2, Appendix 3, and Appendix 4.

Searching other resources

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

- We contacted experts in the field and leading hyperbaric therapy centres (as identified by personal communication and searching the Internet) and asked for additional relevant data in terms of published or unpublished randomised trials.
- We handsearched relevant hyperbaric textbooks (Jain 2016; Mathieu 2006; Neuman 2008; Whelan 2017), journals (*Undersea and Hyperbaric Medicine*, *Hyperbaric Medicine Review*, *South Pacific Underwater Medicine Society (SPUMS) Journal*, *European Journal of Hyperbaric Medicine*, and *Aviation, Space, and Environmental Medicine Journal*) and conference proceedings (Undersea and Hyperbaric Medical Society, SPUMS, European Undersea and Baromedical Society, and International Congress of Hyperbaric Medicine) published since 1980.
- We contacted authors of relevant studies to request details of unpublished or ongoing investigations.
- We examined the reference lists of all trials for inclusion in this review.

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

Data collection and analysis

Selection of studies

Two review authors (MB and RS) scanned the records retrieved by the initial search to identify trials that potentially met the inclusion criteria. The full texts of the potentially eligible articles were retrieved, and the same two review authors independently reviewed the full-text articles to determine if they met the inclusion criteria. In all instances, differences of opinion were to be resolved by discussion among the review authors and referral to a third review author (CM) for a decision. However, this was not necessary.

Data extraction and management

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

Assessment of risk of bias in included studies

We assessed study quality by using an adaptation of the method outlined in Schulz 1995. We have presented results regarding study quality in a descriptive manner. We assessed the following characteristics.

Adequacy of the randomisation process

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

Adequacy of the allocation concealment process

(A) Adequate measures to conceal allocation such as central randomisation; serially numbered, opaque, sealed envelopes; or other description that contained convincing elements of concealment.
(B) Unclearly concealed trials in which there was no mention of allocation concealment approach, or an approach was reported that did not fall into one of the categories in (A).
(C) Inadequately concealed trials in which the method of allocation is not concealed such as alternation methods or use of case record numbers.

Potential for selection bias after allocation

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

Level of masking (treatment provider, participant, outcome assessor)

(A) Double- or triple-blind.
(B) Single-blind.
(C) Non-blind.

Sensitivity analysis

We used a fixed-effect model where there was no evidence of significant heterogeneity between studies and a random-effects model when such heterogeneity was likely (DerSimonian 1986). We considered the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. We tested heterogeneity using the I^2 statistic and assumed significant heterogeneity if I^2 was greater than 40% (more than 40% of the variability in outcome between trials could not be explained by sampling variation) (Higgins 2003). Where appropriate data were available or could be extracted, we intended to compare survival over time using the log hazard ratio (lgHR) and variance (Parmar 1998). For proportions (dichotomous outcomes), we used risk ratio (RR). We would have converted continuous data to the weighted mean difference (WMD) using the inverse variance method and calculated an overall WMD. We tested selection bias using a funnel plot, depending on the number of clinical trials included in the individual outcomes.

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

Where appropriate data existed, we performed subgroup analyses based on:

1. age: adults versus children (less than 16 years);
2. dose of oxygen received (pressure less than 2.5 ATA versus greater than or equal to 2.5 ATA);
3. dose and fractionation of radiation therapy: large fractions (total dose over 12 or fewer fractions) versus conventional fractions (total dose over 12 fractions); and
4. simultaneous versus sequential administration of HBOT.

RESULTS

Description of studies

Results of the search

Our original searches in 2004, 2008, and 2011 identified a combined 286 publications apparently evaluating the use of HBOT in conjunction with therapeutic radiotherapy. A further search in September 2017 located another 266 publications of which, following identification and deletion of duplicate publications, 243 publications were retained. Initial examination of the titles suggested 228 were not relevant to this review, leaving 15 publications, for which the abstracts were retrieved where available. Examination of the abstracts determined that no further relevant studies had been published since our last update in 2011. The total number of studies located from all search periods at each stage is given in Figure 1. Consequently, the number of full reports examined remains at 43 possible comparative trials as in our 2011 update, of which 24 were excluded (see Characteristics of excluded studies table), and the remaining 19 trials included in the review. All 19 trials contributed data to the quantitative meta-analysis (see Figure 1 for the study flow details).

Figure 1. Study flow diagram.

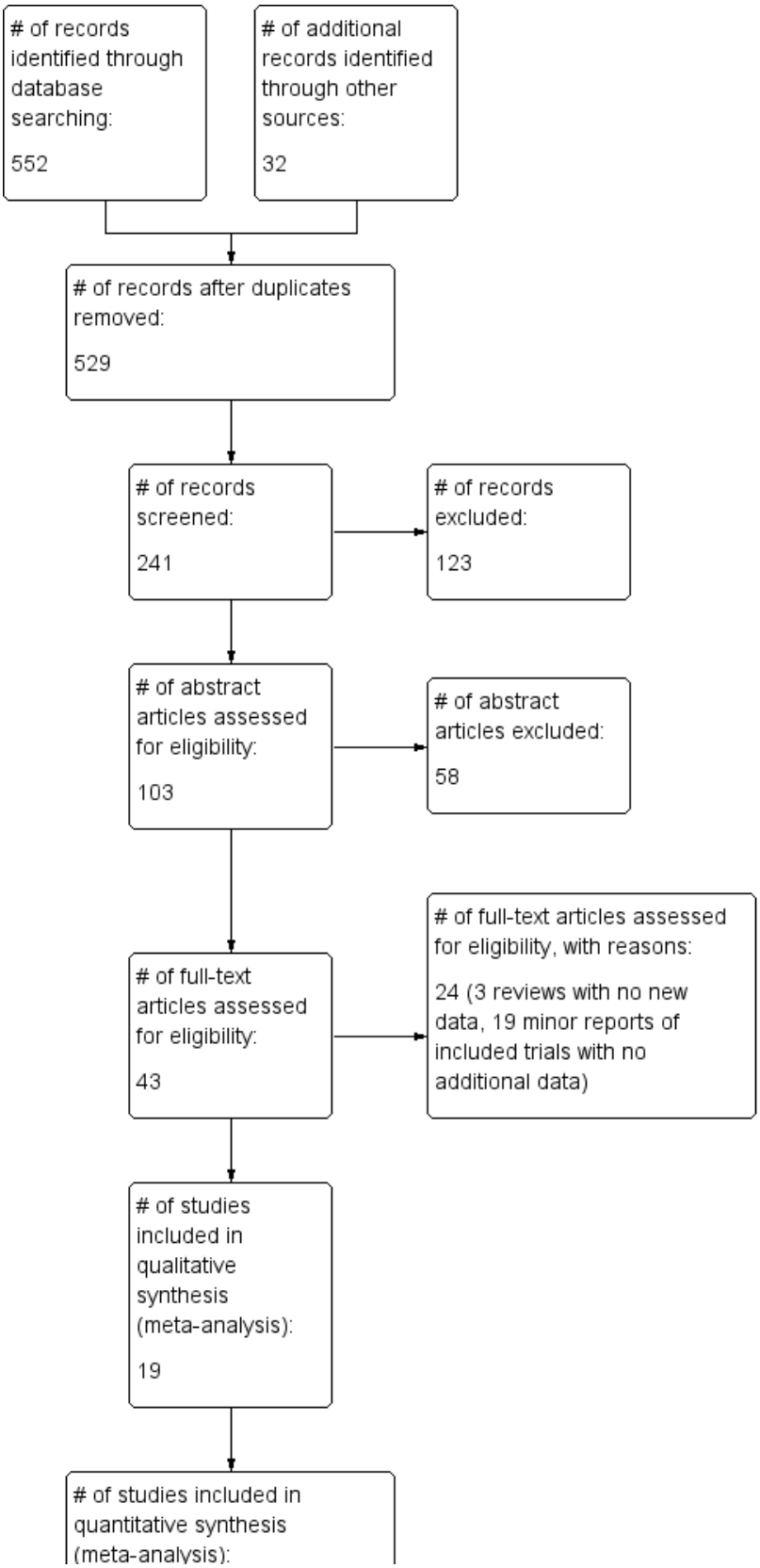
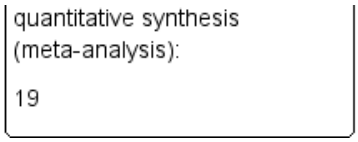


Figure 1. (Continued)



Included studies

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

The dose of oxygen per treatment session in the HBO arm was remarkably uniform, with all trials except one administering external beam radiation therapy at 3 ATA for between 30 and 40 minutes. The exception was Haffty 1999, who used oxygen at 4 ATA and required all participants to be anaesthetised and intubated because of the risk of oxygen toxic seizures. However, the total number of treatment sessions varied widely. The shortest fractionation scheme was two sessions only, separated by three weeks (Haffty 1999); the longest was 40 sessions over eight weeks (Cade 1967; Cade 1978). External beam radiation dose also varied widely in both arms of the studies, with a range from 2600 rads, in Haffty 1999, to 7000 rads, in Shigematsu 1973, for the control groups and from 2300 rads, in Haffty 1999, to 6000 rads, in Cade 1967; Cade 1978, for the HBO groups. Most studies of the treatment of uterine cervical cancer also included intracavity placement of radioactive material, with one exception (Tobin 1971). One trial examined the efficacy of HBO plus a second sensitising agent, misonidazole (Sealy 1986).

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

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

Risk of bias in included studies

Details of the quality assessment are given in the Characteristics of included studies table. In general, we assessed study quality as fair with regard to methodology. The significance of the variations in quality detailed below is unclear, and given that we were able to pool relatively few analyses, we did not use study quality as a basis for sensitivity analysis.

Randomisation

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

Concealment of allocation

Allocation concealment appeared to be adequate for the British Medical Council trials, but none of the remaining studies indicate that the investigators were unable to predict the prospective group to which a participant would be allocated.

Participant baseline characteristics

Participants entered into all trials had proven malignancies for which radiotherapy was the treatment of choice in the anatomical area of interest to the particular trial. Many trials included only participants who were younger than 75 years old. Details of staging are given in the Characteristics of included studies table, but were generally reasonably consistent across trials.

Blinding

None of the included studies were blinded in any way.

Intention-to-treat analysis

Nine studies reported no losses to follow-up (Berry 1979; Cade 1967; Chang 1973; Fletcher 1977; Glassburn 1974; Haffty 1999; Shigematsu 1973; Van Den Brenk 1968; Watson 1978). Two studies reported analysing participants randomised to receive HBO in the control group (Berry 1979; Ward 1979), while 10 studies reported losses to follow-up, none of which appeared in the analysis in those reports. The highest proportion of lost participants was in Plenk 1972, who lost 22 participants at final follow-up, 55% of the total

enrolled. Where possible, we have performed sensitivity analysis using best- and worse-case scenarios for dichotomous outcomes involving those studies with losses to follow-up.

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

Effects of interventions

See: **Summary of findings for the main comparison** Hyperbaric oxygen versus air breathing to enhance the effectiveness of radiotherapy for tumours of the head and neck; **Summary of findings 2** Hyperbaric oxygen compared to air breathing for enhancing the effect of radiation for cancer of the uterine cervix; **Summary of findings 3** Hyperbaric oxygen compared to air breathing for enhancing the effect of radiotherapy for a mixed group of cancers (urinary bladder, lung, rectum, oesophagus, brain)

Primary outcomes

1. Death rate

As all trials reported mortality rate at some time, they all contributed to this outcome. Data were insufficient in any trial to permit calculation of survival over time using the lgHR.

One-year mortality

Mortality at one year with head and neck cancer

Nine trials reported this outcome (Berry 1979; Chang 1973; Haffty 1999; Henk 1977a; Henk 1986; Sealy 1986; Shigematsu 1973; Tobin 1971; Van Den Brenk 1968), for 710 participants after exclusion of withdrawals (31% of the total participants in this review), with 339 (48%) allocated to HBOT and 371 (52%) to control. Over all fractionation schemes, there was a reduction in the proportion of participants dying within one year after receiving radiation therapy with HBOT (risk ratio (RR) of death with HBOT was 0.83, 95% confidence interval (CI) 0.70 to 0.98 (Analysis 1.1). There was no evidence of substantial heterogeneity between trials overall (I^2 = 0%), but we found some heterogeneity for the trials using fewer than 12 sessions of HBO compared to more than 12 using air (I^2 = 39%), so we achieved these results using a random-effects model. There is an absolute risk reduction of 9.2% when using HBOT (number needed to treat for an additional beneficial outcome (to avoid one death) (NNTB) = 11, 95% CI 7 to 52). We assessed the quality of evidence as high.

The reduction in risk of death overall is sensitive to the allocation of withdrawals (best-case scenario: RR 0.73, 95% CI 0.62 to 0.85 (Analysis 1.2); worst-case scenario: RR 0.93, 95% CI 0.76 to 1.15 (Analysis 1.3)). However, the risk for those receiving 12 fractions with HBO versus more than 12 fractions in air is not sensitive to allocation of withdrawals (worst-case scenario: RR 0.72, 95% CI 0.56 to 0.92).

Mortality at one year with cancer of the uterine cervix

Four trials reported this outcome for 728 participants after exclusion of withdrawals (33% of the total participants in this review) (Dische 1999; Tobin 1971; Ward 1979; Watson 1978), with 348 (46%) allocated to HBOT and 384 (54%) to control. There was no clear reduction in the proportion of participants dying within one year after receiving radiation therapy with HBOT (RR 0.88, 95% CI 0.69 to 1.11 (Analysis 1.4)), nor did subgroup analysis suggest any benefit with different fractionation schemes. There was no evidence of substantial heterogeneity between trials overall (I^2 = 0%) using a fixed-effect model. The risk of death was not sensitive to the allocation of withdrawals (best-case scenario: RR 0.87, 95% CI 0.69 to 1.10 (Analysis 1.5); worst-case scenario: RR 0.91, 95% CI 0.72 to 1.15 (Analysis 1.6)). We rated the quality of evidence as high.

Mortality at one year with cancer of the urinary bladder

Four trials reported this outcome for 330 participants after exclusion of withdrawals (14% of the total participants in this review) (Cade 1967; Cade 1978; Plenk 1972; Van Den Brenk 1968), with 165 allocated to both HBOT and control. There was no clear reduction in the proportion of participants dying within one year after receiving radiation therapy with HBOT (RR 0.97, 95% CI 0.74 to 1.27 (Analysis 1.7)), nor did subgroup analysis suggest any benefit with different fractionation schemes. There was moderate heterogeneity between trials overall (I^2 = 39%) (fixed-effect model). The risk of death was not sensitive to the allocation of withdrawals (best-case scenario: RR 0.92, 95% CI 0.71 to 1.21 (Analysis 1.8); worst-case scenario: RR 1.03, 95% CI 0.78 to 1.34 (Analysis 1.9)). We rated the quality of evidence as high.

Mortality at one year with carcinoma of the bronchus

Only one trial reported this outcome (Cade 1967), involving 49 participants after exclusion of withdrawals (2% of the total participants in this review), with 25 (51%) allocated to HBOT and 24 (49%) to control. There was no clear difference in the proportion of participants dying within one year after receiving radiation therapy with HBOT (17 of 25 people died in the HBOT group compared to 15 of 24 people in the air group).

Mortality at one year with carcinoma of the rectum

Only one trial reported this outcome (Tobin 1971), involving four participants (0.2% of the total participants in this review), with two allocated to both HBOT and control. Both participants died following HBOT, while one of those receiving the control died.

Mortality at one year with carcinoma of the oesophagus

Only one trial reported this outcome (Tobin 1971), involving four participants (0.2% of the total participants in this review), with two allocated to both HBOT and control. One participant died following HBOT, and both of those receiving the control died.

Mortality at one year with glioblastoma

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

Mortality at two years

Mortality at two years with head and neck cancer

Three trials reported this outcome for 189 participants after exclusion of withdrawals (8% of the total participants in this review) (Haffty 1999; Sealy 1986; Tobin 1971), with 92 (49%) allocated to HBOT and 97 (51%) to control. Sealy 1986 contributes 65% of the weight to this analysis. There was no clear reduction in the proportion of participants dying within two years after receiving radiation therapy with HBOT (RR 0.97, 95% CI 0.83 to 1.12 (Analysis 2.1)), nor did subgroup analysis suggest any benefit with different fractionation schemes. There was no evidence of

substantial heterogeneity between trials overall (I^2 = 0%) using a fixed-effect model. The reduction in risk of death is not sensitive to the allocation of withdrawals (best-case scenario: RR 0.92, 95% CI 0.79 to 1.07 (Analysis 2.2); worst-case scenario: RR 1.00, 95% CI 0.86 to 1.15 (Analysis 2.3)).

Mortality at two years with cancer of the uterine cervix

Four trials reported this outcome for 607 participants after exclusion of withdrawals (27% of the total participants in this review) (Fletcher 1977; Glassburn 1974; Tobin 1971; Watson 1978), with 294 (48%) allocated to HBOT and 313 (52%) to control. There was no clear reduction in the proportion of participants dying within two years after receiving radiation therapy with HBOT (RR 0.94, 95% CI 0.76 to 1.15 (Analysis 2.4)), neither did subgroup analysis suggest any benefit with different fractionation schemes. There was evidence of moderate heterogeneity between trials overall (I^2 = 36%) (random-effects model). No trials suffered any losses to follow-up after randomisation. We rated the quality of evidence as high.

Mortality at two years with urinary bladder carcinoma

Two trials reported this outcome for 24 participants after exclusion of withdrawals (1% of the total participants in this review) (Plenk 1972; Tobin 1971), with 12 allocated to both HBOT and control. Plenk 1972 contributes 71% of the weight to this analysis. There was no clear difference in the proportion of participants dying within two years after receiving radiation therapy with HBOT (RR 1.57, 95% CI 0.63 to 3.92 (Analysis 2.5)). There was no evidence of substantial heterogeneity between trials overall (I^2 = 0%) (fixed-effect model). The risk of death with HBOT is sensitive to the allocation of the large number of losses to follow-up in the Plenk 1972 trial (best-case scenario: RR 0.47, 95% CI 0.04 to 5.24 (Analysis 2.6); worst-case scenario: RR 5.18, 95% CI 2.18 to 12.31 (Analysis 2.7)). We rated the quality of evidence as moderate, downgrading for imprecision.

Mortality at five years

Mortality at five years with head and neck cancer

Six trials reported this outcome for 550 participants after exclusion of withdrawals (24% of the total participants in this review) (Berry 1979; Chang 1973; Haffty 1999; Henk 1977a; Henk 1986; Sause 1979), with 258 (47%) allocated to HBOT and 292 (53%) to control. Over all fractionation schemes, there was a reduction in the proportion of participants dying within five years after receiving radiation therapy with HBOT (RR 0.82, 95% CI 0.69 to 0.98 (Analysis 3.1)), however subgroup analysis by fractionation scheme suggests the benefit may be restricted to those who receive 12 or fewer fractions when compared to those who receive a standard fractionation scheme of more than 12 sessions (RR in this group 0.69, 95% CI 0.53 to 0.89; RR for 12 or fewer fractions in each group 0.96, 95% CI 0.75 to 1.22). There was moderate heterogeneity between trials overall (I^2 = 37%), however there was little evidence for heterogeneity within each subgroup of fraction schemes (fixed-effect model). There is an absolute risk reduction of 7.5% (NNTB = 14, 95% CI 7 to infinity) overall, but a 20.9% reduction for those who receive 12 or fewer fractions when compared to those who receive a standard fractionation scheme of more than 12 sessions (NNTB = 5, 95% CI 3 to 14). We rated the quality of evidence as high for this outcome.

The overall reduction in risk of death is sensitive to the allocation of withdrawals (best-case scenario: RR 0.77, 95% CI 0.64 to 0.92 (Analysis 3.2); worst-case scenario: RR 0.96, 95% CI 0.81 to 1.13 (Analysis 3.3)), however, the risk for those receiving 12 fractions with HBOT versus more than 12 fractions in air is not sensitive to allocation of withdrawals (worst-case scenario: RR 0.75, 95% CI 0.59 to 0.96).

Mortality at five years with cancer of the uterine cervix

Four trials reported this outcome for 772 participants after exclusion of withdrawals (34% of the total participants in this review) (Brady 1981; Dische 1999; Ward 1979; Watson 1978), with 367 (48%) allocated to HBOT and 405 (52%) to control. There was no significant reduction in the proportion of participants dying within five years after receiving radiation therapy with HBOT (RR 0.95, 95% CI 0.80 to 1.14, P = 0.59 (Analysis 3.4)). There was considerable heterogeneity between trials (I^2 = 63%), for which Watson 1978 is largely responsible (suggesting a strong beneficial effect of HBOT) (random-effects model). The result was not sensitive to the allocation of withdrawals (best-case scenario: RR 0.92, 95% CI 0.77 to 1.09, P = 0.32 (Analysis 3.5); worst-case scenario: RR 0.98, 95% CI 0.81 to 1.18, P = 0.8 (Analysis 3.6)).

Mortality at five years with urinary bladder cancer

Only one trial reported this outcome for 236 participants after exclusion of withdrawals (10% of the total participants in this review) (Cade 1978), with 118 allocated to each of HBOT and control. There was no indication of an important difference in the proportion people dying within five years after receiving radiation therapy with HBOT (with HBOT 85 of 118 were dead at five years, versus 82 of 118 in the air group).

2. Failure to control local tumour

Failure to control local tumour at three months in head and neck cancer

Five trials reported this outcome for 446 participants after exclusion of withdrawals (20% of the total participants in this review) (Chang 1973; Haffty 1999; Henk 1977a; Shigematsu 1973; Van Den Brenk 1968), with 212 (48%) allocated to HBOT and 234 (52%) to control. Over all fractionation schemes, there was an improvement in the chance of local tumour control at three months following radiation therapy with HBOT (RR of failure with HBOT 0.58, 95% CI 0.39 to 0.85 (Analysis 4.1)). Subgroup analysis by fractionation scheme suggests the magnitude of benefit remains similar, but statistical significance is restricted to a comparison between those who receive 12 or fewer fractions in both groups (RR in this group 0.54, 95% CI 0.34 to 0.88; RR for 12 or fewer fractions in HBOT versus more than 12 with control 0.67, 95% CI 0.24 to 1.82). There was moderate heterogeneity between trials overall (I^2 = 26%) (fixed-effect model). We rated the quality of evidence as moderate, downgrading one level for imprecision. There is an absolute risk reduction of 15% when using HBOT (NNTB (to avoid one failure to control) = 7, 95% CI 5 to 17). The overall reduction in failure to control tumour is marginally sensitive to the allocation of withdrawals (best-case scenario: RR 0.57, 95% CI 0.41 to 0.78 (Analysis 4.2); worst-case scenario: RR 0.59, 95% CI 0.35 to 1.00 (Analysis 4.3)).

Secondary outcomes

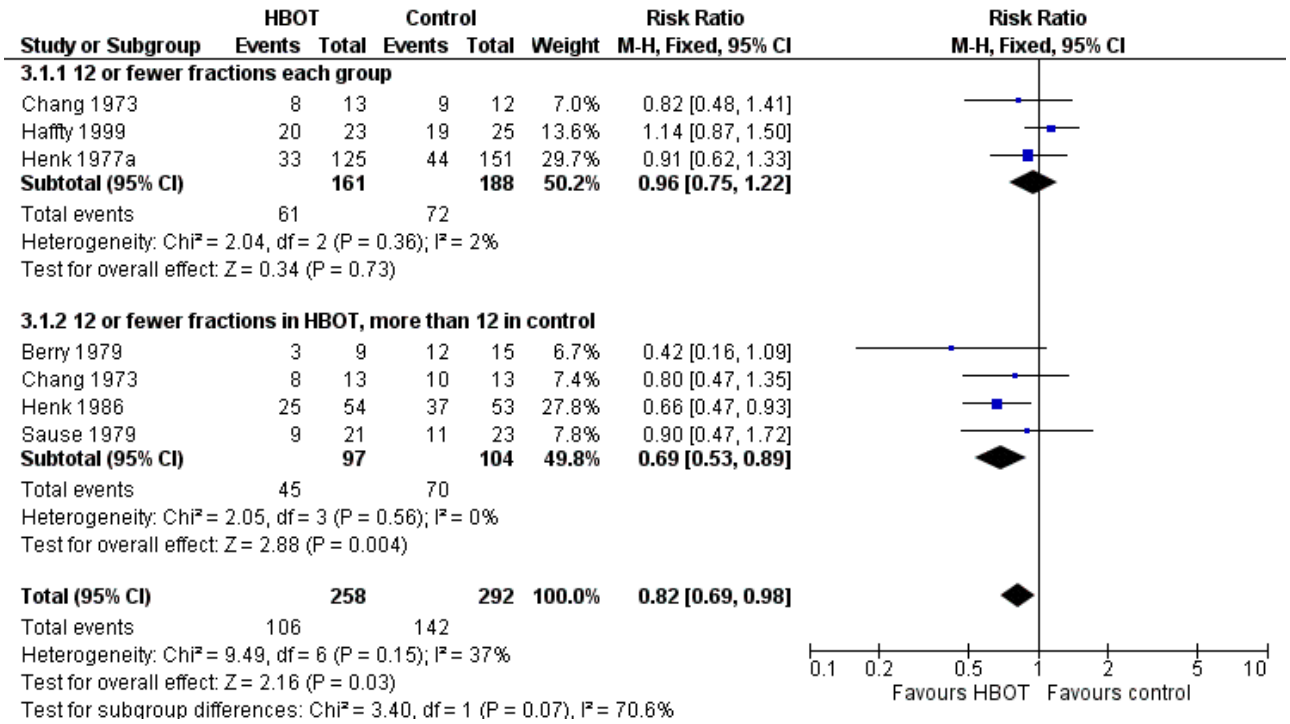
3. Local recurrence

Local recurrence at one year

Local recurrence at one year with head and neck cancer

Five trials reported this outcome for 582 participants after exclusion of withdrawals (31% of the total participants in this review) (Haffty 1999; Henk 1977a; Henk 1986; Sealy 1986; Shigematsu 1973), with 338 (47%) allocated to HBOT and 376 (53%) to control. Over all fractionation schemes, there was a reduction in the incidence of local tumour recurrence following radiation therapy with HBOT (RR 0.66, 95% CI 0.56 to 0.78 (Analysis 5.1)). Subgroup analysis by fractionation scheme suggests the benefit is independent of fractionation scheme (RR with fewer than 12 fractions in each group 0.62, 95% CI 0.50 to 0.77; RR for 12 or fewer fractions in HBOT versus more than 12 with control 0.73, 95% CI 0.56 to 0.94, P = 0.01). There was no evidence of heterogeneity between trials overall (I^2 = 0%) (fixed-effect model). There is an absolute risk reduction of 21.1% when using HBOT (NNTB (to avoid one recurrence) = 5, 95% CI 4 to 8). The overall risk of recurrence is not sensitive to the allocation of withdrawals (best-case scenario: RR 0.61, 95% CI 0.51 to 0.71 (Analysis 5.2); worst-case scenario: RR 0.75, 95% CI 0.65 to 0.87 (Analysis 5.3)) (Figure 2). We rated the quality of evidence as high for this outcome.

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



Local recurrence at one year with cancer of the uterine cervix

Three trials reported this outcome for 714 participants after exclusion of withdrawals (31% of the total participants in this review) (Dische 1999; Ward 1979; Watson 1978), with 338 (47%) allocated to HBOT and 376 (53%) to control. Over all fractionation schemes, there was no clear reduction in the incidence of local tumour recurrence following radiation therapy with HBOT (RR 0.82, 95% CI 0.63 to 1.06 (Analysis 5.4)), with little difference between subgroups with different fractionation schemes. There was evidence of moderate heterogeneity between trials overall (I^2 = 23%), but significant heterogeneity when comparing groups who had received fewer than 12 fractions (I^2 = 46%) (random-effects model). The risk of recurrence was not sensitive to the allocation of those lost to follow-up (best-case scenario: RR 0.81, 95% CI 0.63 to 1.02 (Analysis 5.5); worst-case scenario: RR 0.87, 95% CI 0.63 to 1.19 (Analysis 5.6)). We rated the quality of evidence as high for this outcome.

Local recurrence at two years

Local recurrence at two years with head and neck cancer

Only one trial reported this outcome for 48 participants (2% of the total participants in this review) (Haffty 1999), with 23 (48%) allocated to HBOT and 25 (52%) to control. There was no clear reduction in the incidence of local tumour recurrence following radiation therapy with HBOT (16 of 23 (70%) had recurrence versus 21 of 25 (84%) of those who breathed air) (Analysis 6.1).

Local recurrence at two years with cancer of the uterine cervix

Two trials reported this outcome for 360 participants after exclusion of withdrawals (16% of the total participants in this review) (Glassburn 1974; Watson 1978), with 178 (49%) allocated to HBOT and 182 (51%) to control. Watson 1978 contributes 73% of the weight to this analysis. Over all fractionation schemes, there was a reduction in the incidence of local tumour recurrence following radiation therapy with HBOT (RR 0.60, 95% CI 0.38 to 0.97 (Analysis 6.1)), however subgroup analysis by fractionation scheme suggests the benefit may be restricted to those who received 12 or fewer

fractions in each group (RR in this group 0.53, 95% CI 0.37 to 0.77; RR for more than 12 fractions in each group 0.68, 95% CI 0.26 to 1.73). There was evidence of significant heterogeneity between trials overall (I^2 = 67%) (random-effects model). Overall, there is a risk reduction of 23% when using HBOT (NNTB (to avoid one recurrence) = 5, 95% CI 4 to 8), while the reduction for the comparison between groups receiving fewer than 12 fractions was 41.3% (NNTB = 3, 95% CI 2 to 5). There were no losses to follow-up for any of these studies. We rated the quality of evidence as moderate for this outcome, downgrading for inconsistency between trials.

Local recurrence at five years

Local recurrence at five years with head and neck cancer

Five trials reported this outcome for 495 participants after exclusion of withdrawals (22% of the total participants in this review) (Berry 1979; Haffty 1999; Henk 1977a; Henk 1986; Sause 1979), with 229 (46%) allocated to HBOT and 266 (54%) to control. Over all fractionation schemes, there was a reduction in the incidence of local tumour recurrence following radiation therapy with HBOT (RR 0.77, 95% CI 0.62 to 0.95 (Analysis 7.1)). Subgroup analysis by fractionation scheme suggests the benefit may be restricted to those trials comparing fewer than 12 fractions in each group (RR with fewer than 12 fractions in each group 0.74, 95% CI 0.62 to 0.88; RR for 12 or fewer fractions in HBOT versus more than 12 with control 0.75, 95% CI 0.39 to 1.43). There was evidence of moderate heterogeneity between trials overall (I^2 = 32%), and substantial heterogeneity for those trials comparing fewer than 12 fractions in HBOT with 12 or more fractions in control (I^2 = 63%) (random-effects model). Overall, there is an absolute risk reduction of 19% when using HBOT (NNTB (to avoid one recurrence) = 6, 95% CI 4 to 11); the absolute risk reduction is also 19% for trials comparing fewer than 12 fractions in each group (NNTB = 6, 95% CI 4 to 12).

The overall reduction in local recurrence is sensitive to the allocation of withdrawals (best-case scenario: RR 0.70, 95% CI 0.57 to 0.86 (Analysis 7.2); worst-case scenario: RR 0.84, 95% CI 0.66 to 1.06 (Analysis 7.3)).

Local recurrence at five years with cancer of the uterine cervix

Four trials reported this outcome for 772 participants (34% of the total participants in this review) (Brady 1981; Dische 1999; Ward 1979; Watson 1978), with 367 (48%) allocated to HBOT and 405 (52%) to control. There was no clear reduction in the incidence of local tumour recurrence following radiation therapy with HBOT (RR 0.85, 95% CI 0.65 to 1.13 (Analysis 7.4)). Subgroup analysis did not suggest benefit with any particular fractionation scheme. There was evidence of significant heterogeneity between trials overall (I^2 = 68%) (random-effects model). The analysis is sensitive to the allocation of withdrawals (best-case scenario: RR 0.83, 95% CI 0.72 to 0.97 (Analysis 7.5); worst-case scenario: RR 0.89, 95% CI 0.76 to 1.03 (Analysis 7.6)). We rated the quality of evidence as moderate for this outcome, downgrading for inconsistency.

4. Development of metastasis

Metastases at one year

Metastases at one year with cancer of the uterine cervix

Only one trial reported this outcome for 320 participants (23% of the total participants in this review) (Watson 1978), with 161 (50.3%) allocated to HBOT and 159 (49.7%) to control. There were no withdrawals or losses to follow-up. There was no clear reduction in the incidence of metastases following radiation therapy with HBOT (31 of 161 had metastases with HBOT (19%) versus 39 of 159 when breathing air (25%). Subgroup analysis did not suggest benefit with any particular fractionation scheme.

Metastases at two years

Metastases at two years with cancer of the uterine cervix

Three trials reported this outcome for 522 participants (23% of the total participants in this review) (Fletcher 1977; Glassburn 1974; Watson 1978), with 251 (48%) allocated to HBOT and 271 (52%) to control. There were no withdrawals or losses to follow-up. There was no clear reduction in the incidence of metastases following radiation therapy with HBOT (RR 1.05, 0.84 to 1.31 (Analysis 8.1)). We rated the quality of evidence as high for this outcome.

Metastases at two years with cancer of the urinary bladder

Two trials reported this outcome for 80 participants (2% of the total participants in this review) (Cade 1967; Plenk 1972), with 25 (51%) allocated to HBOT and 24 (49%) to control. However, Plenk 1972 reported no participants with metastases and so did not contribute to the analysis. There were no withdrawals or losses to follow-up. There was no clear increase in the incidence of metastases following radiation therapy with HBOT (RR 2.00, 95% CI 0.58 to 6.91, P = 0.27 (Analysis 8.2)). We rated the quality of evidence as low for this outcome, downgrading by two levels for inconsistency and imprecision.

Metastases at two years with cancer of the bronchus

Only one trial reported this outcome for 49 participants (3.5% of the total participants in this review) (Cade 1967), with 39 (51%) allocated to HBOT and 41 (49%) to control. There were no withdrawals or losses to follow-up. There was no important difference in the incidence of metastases following radiation therapy with HBOT (13/25 (52%) in the HBOT group versus 12/24 (50%) in the air group).

Metastases at five years

Metastases at five years with cancer of the head and neck

One trial reported this outcome for 50 participants (2% of the total participants in this review) (Chang 1973), with 26 (52%) allocated to HBOT and 24 (48%) to control. There were no withdrawals or losses to follow-up. There was no clear reduction in the incidence of metastases following radiation therapy with HBOT (2/26 participants (8%) versus 4/24 participants (17%) treated in air) (Analysis 9.1).

Metastases at five years with cancer of the uterine cervix

Three trials reported this outcome for 456 participants after exclusion of withdrawals (20% of the total participants in this review) (Brady 1981; Ward 1979; Watson 1978), with 221 (49%) allocated to HBOT and 235 (51%) to control. Watson 1978 contributes 83% of the weight of this analysis. Over all fractionation schemes, there was no clear difference in the incidence of metastases following radiation therapy with HBOT (RR 0.79, 0.50 to 1.26 (Analysis 9.2)). Subgroup analysis by fractionation scheme suggests there may be a benefit when comparing 12 or fewer fractions in each group (RR 0.67, 95% CI 0.45 to 0.99), but not for other comparisons (RR with 12 or fewer fractions with HBOT versus

more than 12 with control RR 0.07, 95% CI 0.00 to 1.12 and RR for more than 12 fractions in each group 0.99, 95% CI 0.78 to 1.26). There was evidence of considerable heterogeneity between trials overall (I^2 = 58%) (random-effects model).

The risk of metastases was not sensitive to the allocation of those lost to follow-up (best-case scenario: RR 0.76, 95% CI 0.46 to 1.26 (Analysis 9.3); worst-case scenario: RR 0.85, 95% CI 0.56 to 1.31 (Analysis 9.4)).

5. Quality of life

No studies reported on the outcome.

6. Adverse effects

Death from radiation tissue effects

Two trials reported this outcome for 633 participants after exclusion of withdrawals (28% of the total participants in this review) (Dische 1999; Watson 1978), with 307 (49%) allocated to HBOT and 326 (51%) to control. There was no clear increase in the chance of death due to radiation tissue injury following HBOT (RR 1.64, 95% CI 0.89 to 3.03 (Analysis 10.1)).

Severe radiation tissue injury

Seven trials reported this outcome for 779 participants after exclusion of withdrawals (34% of the total participants in this review) (Brady 1981; Haffty 1999; Henk 1986; Sause 1979; Sealy 1986; Watson 1978; Ward 1979), with 379 (48%) allocated to HBOT and 400 (52%) to control. There was an increase in the chance of severe radiation tissue injury following HBOT (RR 2.35, 95% CI 1.66 to 3.33, I^2 = 15% (Analysis 10.2)). There is an absolute risk increase of 12% when using HBOT (number needed to treat for an additional harmful outcome (NNTH) to cause one severe injury = 8, 95% CI 4 to 15).

For cancer of the head and neck, four trials reported this outcome including a total of 323 participants (Haffty 1999; Henk 1986; Sause 1979; Sealy 1986). There was an increased chance of severe radiation injury following HBOT (RR 2.64, 95% CI 1.65 to 4.23, I^2 = 1%).

For cancers of the uterine cervix, three trials reported this outcome including a total of 456 participants (Brady 1981; Ward 1979; Watson 1978). There was an increased chance of severe radiation injury when HBOT was used (RR 2.05 95%CI 1.22 to 3.46, I2 = (1.22 to 1.46, I^2 = 42%).

The increased risk of injury is not sensitive to the allocation of withdrawals (best-case scenario: RR 1.94, 95% CI 1.39 to 2.69 (Analysis 10.3); worst-case scenario: RR 2.69, 95% CI 1.92 to 3.77 (Analysis 10.4)).

Acute central nervous system toxicity

Four trials reported this outcome for 331 participants after exclusion of withdrawals (15% of the total participants in this review) (Cade 1967; Chang 1973; Plenk 1972; Sealy 1986), with 150 (45%) allocated to HBOT and 181 (55%) to control. There was an increase in the chance of acute central nervous toxicity following HBOT (RR 6.76, 95% CI 1.16 to 39.31, I^2 = 0% (Analysis 10.5)). There is an absolute risk increase of 5% when using HBOT (NNTH to cause one episode = 22, 95% CI 11 to 44). The increased risk of injury is sensitive to the allocation of withdrawals (best-case scenario: RR 3.00, 95% CI 0.81 to 11.10 (Analysis 10.6); worst-case scenario: RR 9.74, 95% CI 1.73 to 54.98 (Analysis 10.7)).

For cancers of the head and neck, two trials reported this outcome including a total of 267 participants (Chang 1973; Sealy 1986). The was no clear increase in the risk of seizure in this subgroup of participants (RR 4.3, 95% CI 0.47 to 39.6, I^2 = 0%).

Middle ear barotrauma

Only one trial reported this outcome for 89 participants (4% of the total participants in this review) (Cade 1967), with 45 allocated to HBOT and 44 to control. There were no losses to follow-up or withdrawals. Despite there being no recorded episodes of barotrauma when breathing air, the chance of suffering middle ear barotrauma was not clearly increased with HBOT (3 of 45 (7%) versus zero of 44 (0%)) (Analysis 10.8).

DISCUSSION

Summary of main results

We were able to pool data for a number of clinical outcomes of interest, however interpretation of some results was complicated by consideration of the fractionation scheme through subgroup analysis. In general, HBO exposure during irradiation was more beneficial when the total dose of radiation was delivered in low numbers of fractions (12 or fewer) than when a more conventional 20- to 25-fraction scheme was used. Any possible benefit of HBO must therefore be interpreted in the context of the most effective fractionation scheme in air.

For head and neck cancer, there was an overall reduction in the risk of dying at both one year and five years after therapy (RR 0.83, 95% CI 0.70 to 0.98, I^2 = 0%, NNTB = 11 and RR 0.82, 95% CI 0.69 to 0.98, I^2 = 37%, NNTB = 5, respectively; high-quality evidence), and some evidence of improved local tumour control immediately following irradiation (RR with HBOT 0.58, 95% CI 0.39 to 0.85, I^2 = 30%, NNTB = 7; moderate-quality evidence only due to imprecision). There was also a lower incidence of recurrence of tumour when using HBOT at both one and five years (RR at one year 0.66, 95% CI 0.56 to 0.78, I^2 = 0%, NNTB = 5, high-quality evidence; RR at five years 0.77, 95% CI 0.62 to 0.98, I^2 = 32%, NNTB = 6, moderate-quality evidence due to inconsistency between trials). No trials reported either the risk of developing metastases or quality of life assessment. Any benefits come at the cost of an increased risk of adverse effects with HBOT (severe radiation reaction RR 2.64, 95% CI 1.65 to 4.23, I^2 = 1%, high-quality evidence; seizures from acute oxygen toxicity RR 4.3, 95% CI 0.47 to 39.6, I^2 = 0%, moderate-quality evidence due to imprecision). There was some evidence from a single trial for a reduction in the chance of metastases at five years after treatment, but with considerable uncertainty (RR with HBOT 0.45 95% CI 0.09 to 2.30, moderate quality evidence). Summary of findings for the main comparison.

For carcinoma of the uterine cervix, there was no clear benefit in terms of mortality at either one year or five years (RR with HBOT at one year 0.88, 95% CI 0.69 to 1.11, I^2 = 0%, high-quality evidence; RR at five years 0.95, 95% CI 0.80 to 1.14, I^2 = 63%, moderate-quality evidence due to inconsistency between trials). Similarly, there was no clear evidence of a benefit of HBOT in the rate of recurrence reported (RR with HBOT at one year 0.82, 95%

CI 0.63 to 1.06, I^2 = 23%, high-quality evidence; RR at five years 0.85, 95% CI 0.65 to 1.13, I^2 = 68%, moderate-quality evidence due to inconsistency between trials). We also found no clear evidence for any effect of HBOT on the rate of development of metastases at two years (RR with HBOT 1.05, 95% CI 0.84 to 1.31, I^2 = 0%, high quality evidence) or at five years (RR with HBOT 0.79, 95% CI 0.05 to 1.26, I^2 = 58%, moderate quality evidence downgraded due to inconsistency). There were, however, increased adverse effects with HBOT. The risk of a severe radiation injury at the time of treatment with HBOT was 2.05, 95% CI 1.22 to 3.46, I^2 = 42%, high-quality evidence. No trials reported any failure of local tumour control, quality of life assessments, or the risk of seizures during treatment. Summary of findings 2

Regarding treatment of urinary bladder cancer, there was no clear evidence of a benefit from HBOT at one year (RR 0.97, 95% CI 0.74 to 1.27, I^2 = 26%, high-quality evidence), nor any benefit in the risk of developing metastases at two years (RR 2.0, 95% CI 0.58 to 6.91, moderate-quality evidence, downgraded for imprecision). No trial reported on failure of local control, local recurrence, quality of life, or adverse effects. Summary of findings 3.

When all cancer types were combined, there was evidence for an increased risk of severe radiation tissue injury during the course of radiotherapy with HBOT (RR 2.45, 95% CI 1.85 to 3.24, I^2 = 2%, NNTH = 8, high-quality evidence) and of oxygen toxic seizures during treatment (RR with HBOT 6.8, 96% CI 1.2 to 39.3, I^2 = 0%, NNTH = 22, moderate-quality evidence due to imprecision). Summary of findings 3.

Overall completeness and applicability of evidence

A total of 2286 participants were available for evaluation using our planned comparisons. There were 785 participants with head and neck tumours, 1089 with carcinoma of the cervix, and 343 with carcinoma of the bladder. While there were sufficient numbers to form some impression of treatment impact for these tumours, there were only 49 participants with carcinoma of the bronchus and four each of glioblastoma, carcinoma of the rectum, and carcinoma of the oesophagus. The trials in this review therefore have low power to assess the impact of HBO on these tumours.

We included data from 19 trials investigating the treatment of various malignancies with radiation therapy while breathing HBO, and we believe these represent all randomised human trials in this area, both published and unpublished, at the time of our search of the databases. We did not locate further trials when we repeated the searches in September 2008, March 2011, and September 2017. Ten trials included participants with head and neck cancers, seven trials of carcinoma of the uterine cervix, five trials of carcinoma of the urinary bladder, and one trial each of carcinoma of the bronchus, glioblastoma, cancer of the oesophagus, and cancer of the rectum. We found some evidence that radiotherapy with HBO reduces the one- and five-year mortality rate and local tumour recurrence, along with improved early local tumour control for head and neck cancer, and two-year local recurrence for carcinoma of the cervix. We also found evidence of significant adverse effects with HBOT, particularly the incidence of oxygen toxic seizures and the chance of suffering severe radiation injury. There were no reliable data from these trials to confirm any beneficial effect of HBOT for other malignancies studied, nor on the incidence of metastatic disease for cancers of any primary site.

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

Quality of the evidence

Although study quality varied across the included trials, in general the methodology was reasonable, as 13 of the 19 included trials employed a reliable method of randomisation and allocation concealment. Although none of the trials employed a sham therapy, most of our clinical outcomes, such as mortality and cancer recurrence, were unlikely to be subject to participant or observer bias. The quality of the evidence was generally high or moderate for the primary outcomes (assessed using the GRADEpro GDT 2015 methodology). Some major problems of this review were the poor reporting of methodological quality in some of the included trials, variability in entry criteria, the nature and timing of outcomes, and poor reporting of outcomes. In particular, there is a possibility of bias due to different fractionation schemes and radiation doses across the trials, as well as a general failure to report data suitable for comparison of survival over time using the lgHR. None of the trials blinded participants, investigators, or outcome assessors to treatment.

Potential biases in the review process

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

Agreements and disagreements with other studies or reviews

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

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence that hyperbaric oxygenation therapy (HBOT) improves local tumour control and mortality for cancers of the head and neck, as well as reducing the chance of local tumour recurrence in cancers of the head, neck, and uterine cervix. However, there is also some evidence that these outcomes may be related to the use of unusual fractionation schemes, and these benefits should be interpreted with caution. Hyperbaric oxygenation therapy also appears to be associated

with significant adverse effects including oxygen toxic seizures and severe tissue radiation injury. Given the methodological and reporting inadequacies of the primary studies included in this review, our results demand a cautious interpretation.More research is needed for head and neck cancer, but is probably not justified for uterine cervical or bladder cancer. There is little evidence available concerning malignancies at other anatomical sites.

Implications for research

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

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

ACKNOWLEDGEMENTS

We thank Gail Quinn and Clare Jess (Managing Editors) of the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group for their assistance in the preparation of this review. Joanne Platt (Information Specialist) for designing and executing the search strategy. We are particularly grateful for the extensive editorial assistance of Heather Dickinson for the original review.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS), or the Department of Health.

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CHARACTERISTICS OF STUDIES

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

Berry 1979

Methods	RCT with allocation concealment and randomisation through central sealed-envelope allocation. Participant, outcome assessors, and treating team all aware of allocation at the start of treatment. No indication of power calculation
Participants	24 adults with SCC of the head and neck where radiotherapy was the treatment of choice. 11 allocated to HBOT and 13 to control. No dropouts, but 2 participants crossed from HBOT to control after refusing HBOT.
Interventions	• Control: between 4450 and 5500 rads in 15 or 20 fractions over 3 weeks • HBOT: 400 to 4500 rads in 10 fractions over 3 weeks, pressure and time not specified but likely to have been 3 ATA for 30 to 40 minutes total exposure time
Outcomes	Death at 1 and 5 years, local recurrence at 5 years
Notes	See also Berry 1978.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not clearly described but overseen by MRC: "Randomisation was done by MRC."
Allocation concealment (selection bias)	Low risk	"The MRC Working Party (1978) ... provided randomisation to air or HBO ..."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No evidence of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants reported.
Selective reporting (reporting bias)	Unclear risk	No pre-trial reporting plan available.
Other bias	Unclear risk	2 participants allocated to HBO were treated and analysed in the air group.

Brady 1981

Methods	RCT with allocation concealment not clear, method of randomisation not stated. Participant, outcome assessors, and treating team all aware of allocation. No indication of power calculation
Participants	65 adults with stage IIb to IVa carcinoma of the uterine cervix where radiotherapy was the treatment of choice. 34 allocated to HBOT and 31 to control. Several participants refused HBOT; only 19 of 34 available for analysis in HBOT group and 29 of 31 in the control group.
Interventions	• Control: 5000 rads by external beam in 25 fractions over 5 weeks plus radium implants where possible • HBOT: 4000 rads in 10 fractions over 5 weeks with intracavitary implants where possible. All external beam radiotherapy conducted at 3 ATA breathing 100% oxygen, total compression time about 40 minutes.
Outcomes	Death at 4 years, local recurrence at 4 years, metastases at 4 years, late radiation tissue injuries
Notes	Trial stopped due to poor accrual.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	High risk	"Seven randomised patients could not be evaluated ... one refused to sign the consent."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No relevant statement in paper
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt to blind personnel or participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Seven of 65 patients randomised patients could not be evaluated."
Selective reporting (reporting bias)	Unclear risk	"Over 90% of the patients have been followed ..."
Other bias	Unclear risk	No other clear risk identified.

Cade 1967

Methods	RCT with allocation concealment and randomisation by centrally generated card method. 2 separate studies reported - one for carcinoma of the bronchus and one for carcinoma of the urinary bladder.

Cade 1967 *(Continued)*

	Participant, outcome assessors, and treating team all aware of allocation at start of therapy course. No indication of power calculation
Participants	• Trial 1: 49 adults with carcinoma of the bronchus, 25 allocated to HBOT and 24 to control • Trial 2: 40 adults with carcinoma of the urinary bladder with spread confined to the pelvis, 20 allocated to each of HBOT and control No dropouts or losses to follow-up in either trial
Interventions	• Control: 6000 rads by external beam in 40 fractions over 8 weeks • HBOT: identical radiotherapy schedule conducted at 3 ATA breathing 100% oxygen, total compression time about 40 minutes
Outcomes	Death 1 year, metastatic disease 1 to 2 years, oxygen toxicity data (combined for both trials)
Notes	Also reported in McEwen 1968

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients are selected randomly for treatment in air or hyperbaric oxygen by drawing a card provided by the Medical Research Council's statistical division."
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Both groups receive identical radiotherapy"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence of outcome assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants reported.
Selective reporting (reporting bias)	Unclear risk	No pre-trial reporting plan available.
Other bias	Unclear risk	No evidence of other biases

Cade 1978

Methods	Multicentred RCT with allocation concealment and randomisation by centrally generated envelope method. Participant, outcome assessors, and treating team all aware of allocation at start of therapy course. No indication of power calculation

Cade 1978 *(Continued)*

Participants	241 adults with carcinoma of the urinary bladder spread to vagina or rectum. Losses not accounted for, final analysis 118 in each group (5 lost).

Interventions	Different treatment regimens were used in each of the 4 centres and also varied within some centres during the course of the trial. No individual centre or fractionation data provided.
	• Control:
	  * 1A. Portsmouth 65 participants: 6000 rads in 40 fractions over 8 weeks
	  * 1B. Portsmouth 57 participants: 3600 rads in 6 fractions over 2.5 weeks
	  * 2. Oxford 25 participants: 4250 rads in 10 fractions over 4.5 weeks
	  * 3.Glasgow 27 participants: 4500 rads in 24 fractions over 7 weeks
	  * 4A. Mount Vernon 41 participants: 6000 rads in 30 fractions over 6 weeks
	  * 4B. Mount Vernon 26 participants: 4725 rads in 15 fractions over 4.5 weeks
	• HBOT: same regimen, with all external beam radiotherapy conducted while breathing 100% oxygen at 3 ATA for approximately 30 minutes

Outcomes	Death at 1 and 5 years
Notes	See also second publication of this study (Wiernik 1974) referenced under Cade 1978 and Kirk 1976,Wiernik 1974, and Dische 1973.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not specified but carried out by central authority and delivered in sealed envelopes
Allocation concealment (selection bias)	Low risk	"they were allocated to treatment in oxygen or in air by opening a sealed envelope containing instructions prepared by the Medical Research Council Statistical Research and Services Unit."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No indication of any attempt to blind participants or therapists
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No indication of any attempt to blind participants or therapists
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Mortality was only outcome and no evidence of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of outcome data
Selective reporting (reporting bias)	Unclear risk	No prior reporting plan available.
Other bias	Low risk	No evidence of other bias

Chang 1973

Methods	RCT with allocation concealment and randomisation through sealed-envelope method. Participant, outcome assessors, and treating team all aware of allocation at the start of treatment. No indication of power calculation
Participants	51 previously untreated adults with advanced (T3 and T4) carcinomas of the soft palate and adjacent structures. 26 allocated to HBOT and 25 to control. No dropouts or losses to analysis

Interventions	• Control: 2 regimens
	  * 6000 rads in 30 fractions over 6 weeks
	  * 4200 rads in 7 fractions over 3.5 weeks
	• HBOT: 3600 rads in 6 fractions over 3 weeks while breathing 100% oxygen at 3 ATA for approximately 30 minutes

Outcomes	Death at 1 and 5 years, early local tumour control, metastatic disease at 5 years, oxygen toxicity. Hyperbaric oxygen therapy group results split between the 2 controls for analysis.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation with sealed envelope technique"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No evidence of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence of outcome assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participant outcomes reported.
Selective reporting (reporting bias)	Unclear risk	No pre-trial outcome reporting plan available.
Other bias	Unclear risk	2 control groups using different dosing schemes

Dische 1999

Methods	RCT with allocation concealment and randomisation by centrally generated envelope method. Participant, outcome assessors, and treating team all aware of allocation. No indication of power calculation

Dische 1999 *(Continued)*

Participants	335 adults with stage IIb or III carcinoma of the uterine cervix where radiotherapy was the treatment of choice. 146 allocated to HBOT and 170 to control. 19 participants lost to follow-up; group not indicated.

Interventions	4 different treatment regimens used. Where individual centre data are given, they are used in analysis.
	• Control:
	  * 88 participants: 4500 rads in 10 fractions over 5 weeks
	  * 82 participants: 5800 rads in 27 fractions over 5.5 weeks (some participants also had intracavitary treatment)
	• HBOT: 2 groups received the same radiotherapy but while at 3 ATA breathing oxygen for approximately 30 minutes

Outcomes	Death 1 and 5 years, locoregional control 1 and 5 years, death by late radiation effects at 5 years
Notes	See also Bennett 1978. 27-fraction HBOT schema discontinued after interim analysis did not suggest any benefit.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Remote randomisation by "Medical Research Council Statistical Unit".
Allocation concealment (selection bias)	Unclear risk	"Randomisation was performed by opening of envelopes ...". No mention of time of enrolment
Blinding (performance bias and detection bias) All outcomes	Low risk	"Treatment planning was similar for all patients"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt to blind participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear if this was done. Hard outcome of death
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 10 participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No prior outcome planning published.
Other bias	Low risk	No evidence of other biases

Fletcher 1977

Methods	RCT stratified for node involvement and clinical stage, with allocation concealment not clear, method of randomisation not stated. Participant, outcome assessors, and treating team all aware of allocation. No indication of power calculation

Fletcher 1977 *(Continued)*

Participants	233 adults with stage IIb to IVa carcinoma of the uterine cervix where radiotherapy was the treatment of choice. 109 allocated to HBOT and 124 to control. No dropouts or losses to follow-up
Interventions	• Control: between 4000 and 5500 rads by external beam in 20 to 35 fractions over 4 to 5 weeks plus radium implant in more advanced cases • HBOT: same regimen, with all external beam radiotherapy conducted at 3 ATA breathing 100% oxygen, total compression time about 40 minutes
Outcomes	Death at 2 years, metastatic disease at 2 years
Notes	An interim report that does not seem to have been reported in a complete paper to date. See also Lindberg 1973 and Fletcher 1975.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Statified by tumour staging but method not clear
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	Same treatment was applied to both groups. "The size of the external beam portal was determined by the status of the nodes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of participants reported.
Selective reporting (reporting bias)	Unclear risk	No prior outcome reporting plan available.
Other bias	Unclear risk	Radiation doses changed several times during the course of the trial.

Glassburn 1974

Methods	RCT with allocation concealment not clear, method of randomisation not stated. Participant, outcome assessors, and treating team all aware of allocation. No indication of power calculation. Individuals excluded if second primary, prior radiotherapy, or contraindication to HBOT.
Participants	40 adults with stage III or IV carcinoma of the uterine cervix where radiotherapy was the treatment of choice. 17 allocated to HBOT and 23 to control. No dropouts or losses to follow-up
Interventions	• Control: 6000 external beam in 24 fractions over 6 weeks plus radium implant

Glassburn 1974 *(Continued)*

	• HBOT: same regimen, but dose reduced by 7% after first 6 participants displayed high rate of gastrointestinal complications. All external beam radiotherapy conducted at 3 ATA breathing 100% oxygen, total compression time about 40 minutes.
Outcomes	Death at 27 months, local tumour recurrence at 27 months, metastases at 27 months
Notes	An interim report that does not seem to have been reported in a complete paper to date. See also Faust 1970, added as second reference under Glassburn 1974

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given.
Allocation concealment (selection bias)	Unclear risk	No details given.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No evidence of detection bias, but see 'other bias' below.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt to blind personnel or participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for.
Selective reporting (reporting bias)	Unclear risk	No prior outcome reporting plan available.
Other bias	High risk	Radiation regimen changed during the trial due to complications. "Because of these complications the ... dose of was decreased by 7% in the hyperbaric group."

Haffty 1999

Methods	RCT using sealed envelopes, but allocation concealment not clear. Participant, outcome assessors, and treating team all aware of allocation after start of therapy.
Participants	48 adults with SCC of the head and neck where radiotherapy was the treatment of choice. 23 allocated to HBOT and 25 to control.
Interventions	• Control: 2530 rads in 2 fractions over 2 weeks • HBOT: 2300 rads in 2 fractions over 2 weeks, while anaesthetised and intubated breathing 100% oxygen at 4 ATA for 30 to 40 minutes total exposure time

Haffty 1999 *(Continued)*

Outcomes	Death at 1, 2, and 5 years, local tumour control, recurrence rate, complications
Notes	Very unusual radiation regimen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"they were randomised with a simple 'lucky envelope' drawing to treatment"
Allocation concealment (selection bias)	Unclear risk	"Once patients were screened and declared eligible for the trial, they were randomised"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No evidence of performance or detection bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded. "the complete medical record ... were reviewed in detail"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data: "we can report complete long-term outcome".
Selective reporting (reporting bias)	Unclear risk	No prior outcome plan available.
Other bias	Unclear risk	Trial stopped early "when it became clinically apparent that the response rates were superior with HBO-4".

Henk 1977a

Methods	RCT stratified by site of tumour (nasal and oral, laryngeal, laryngopharyngeal and other) with allocation concealment not clear, method of randomisation not stated. Participant, outcome assessors, and treating team all aware of allocation. No indication of power calculation
Participants	295 adults with SCC of the head and neck where radiotherapy was the treatment of choice. 143 allocated to HBOT and 152 to control. Dropouts identified (18 from HBOT group, 1 from control group) but not included in analysis.
Interventions	• Control: between 3500 and 4500 rads in 10 fractions over 3 weeks • HBOT: same regimen, pressure and time not specified but likely to have been 3 ATA for 30 to 40 minutes total exposure time
Outcomes	Death at 1 to 5 years, local control of tumour at 3 months, local recurrence rates at 1 to 5 years, significant radiation tissue effects at 6 months
Notes	Other reports of this trial in Henk 1974, Henk 1975, Kunkler 1968.

Henk 1977a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	"... the radiotherapy treatment volume was decided and the tumour dose prescribed before randomisation"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt at blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In HBO group, 10 could not complete treatment but were analysed in the HBO group. A further 18 could not be compressed for various reasons and were excluded after randomisation.
Selective reporting (reporting bias)	Unclear risk	No prior analysis plan available.
Other bias	Low risk	No other bias evident.

Henk 1986

Methods	RCT stratified by site of tumour (mouth, oropharynx, nasal sinus, nasopharynx, larynx, hypopharynx, and middle ear). Allocation concealment and randomisation achieved by centrally supplied sealed envelopes. Participant, outcome assessors, and treating team all aware of allocation after trial started. No indication of power calculation
Participants	107 adults with SCC of the head and neck where radiotherapy was the treatment of choice. 54 allocated to HBOT and 53 to control. Dropouts identified (1 from HBOT group) but not included in analysis.
Interventions	• Control: 6400 rads in 30 fractions over 6 weeks • HBOT: 4100 rads in 10 fractions over 3 weeks, pressure and time not specified but likely to have been 3 ATA for 30 to 40 minutes total exposure time
Outcomes	Death at 1 and 5 years, recurrence at 1 and 4 years, late radiation tissue effects at 5 years
Notes	Other reports of this trial in Henk 1974, Henk 1975, Henk 1977a.

Risk of bias

Bias	Authors' judgement	Support for judgement

Henk 1986 *(Continued)*

Random sequence generation (selection bias)	Low risk	"... randomly allocated ... using sealed envelopes provided by the Medical Research Council Statistical Unit."
Allocation concealment (selection bias)	Unclear risk	Not clear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No evidence of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No attempt to blind outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number reaching final follow-up unclear.
Selective reporting (reporting bias)	Unclear risk	No pre-trial outcome reporting plan available.
Other bias	Unclear risk	No indication of other biases

Plenk 1972

Methods	RCT using random number table, allocation concealment not clear. Participant, outcome assessors, and treating team all aware of allocation. No indication of power calculation
Participants	40 adults with carcinoma of the urinary bladder. 19 allocated to HBOT and 21 to control. More than 50% loss to follow-up at 2 years
Interventions	• Control: 6000 rads in 24 to 30 fractions over 6 weeks • HBOT: 4800 rads in 12 fractions over about 4 weeks at 3 ATA breathing oxygen for about 40 minutes
Outcomes	Death at 1 and 2 years, oxygen toxicity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Assignment ... by numbered cards selected from random tables."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias)	Unclear risk	Different irradiation treatment plans in each group

Plenk 1972 *(Continued)*

All outcomes		
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence that outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	No pre-trial reporting plan available.
Other bias	Unclear risk	No evidence of other biases

Sause 1979

Methods	RCT of previously untreated head and neck SCC with allocation concealment not clear, method of randomisation not stated. Participant, outcome assessors, and treating team all aware of allocation. No indication of power calculation
Participants	50 adults with SCC of the head and neck where radiotherapy was the treatment of choice. Group allocation unclear, but 6 dropouts and 21 analysed in HBOT group, 23 in control.
Interventions	• Control: total dose 6250 rads in 25 fractions over 6 weeks • HBOT: total dose 4800 rads in 12 fractions over 5 weeks while breathing oxygen at 3 ATA for about 30 minutes
Outcomes	Death at 2 to 8 years, local tumour control, and late radiation tissue injury
Notes	5 participants excluded from analysis because they died from "intercurrent disease" prior to 2-year follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"Patients ... who agreed, were randomised ..."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No evidence of bias
Blinding of participants and personnel (performance bias)	Unclear risk	No attempt to blind participants or personnel

Sause 1979 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence given.
Incomplete outcome data (attrition bias) All outcomes	High risk	"Omitted from this analysis are five patients who died of intercurrent disease ..."
Selective reporting (reporting bias)	Unclear risk	No prior reporting plan available.
Other bias	Unclear risk	No clear other biases.

Sealy 1986

Methods	RCT stratified by sex, site of tumour, extent of node involvement, and histology. Allocation concealment achieved by sealed envelopes prepared by an individual not otherwise involved in the study. Participant, outcome assessors, and treating team all aware of allocation. No indication of power calculation
Participants	130 adults with SCC of the mouth or fixed lymph nodes in the neck where radiotherapy was the treatment of choice. 64 allocated to HBOT and 66 to control. Dropouts identified (4 from HBOT group, 2 from control) but not included in analysis.
Interventions	• Control: 6300 rads in 30 fractions over 6 weeks • HBOT: 3600 rads in 6 fractions over 2.5 weeks at 3 ATA for 30 to 40 minutes total exposure time, plus misonidazole 2 grams per square metre body surface at the time of each fraction
Outcomes	Death at 1 and 2 years, local recurrence at 1 year, toxic reactions to therapy and oxygen toxicity
Notes	Other report of this trial in Sealy 1978.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was by means of previously prepared batches of sealed envelopes. The person preparing and drawing the envelope was not the clinician concerned."
Allocation concealment (selection bias)	Low risk	"Informed consent sought prior to randomisation"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No evidence of performance or detection bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt to blind participants or personnel
Blinding of outcome assessment (detection bias)	Unclear risk	Not mentioned

Sealy 1986 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 participants withdrawn after randomisation.
Selective reporting (reporting bias)	Unclear risk	No pre-trial reporting plan
Other bias	Unclear risk	No evidence of other bias

Shigematsu 1973

Methods	RCT stratified by tumour stage, and it is possible that allocation was actually achieved by quasi-random method. No indication of allocation concealment. Participant, outcome assessors, and treating team all aware of allocation after treatment started. No indication of power calculation
Participants	42 adults with SCC of the maxillary sinus. 21 allocated to both HBOT and control. No dropouts from therapy or losses to follow-up. All participants had myringotomies prior to compression.
Interventions	• Control: 6000 to 7000 rads 8 or 10 fractions over 4 to 5 weeks • HBOT: 4000 to 5000 rads on the same schedule at 3 ATA for 20 to 30 minutes total exposure time
Outcomes	Death at 1 year, local early tumour control, recurrence at 1 year
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly stated, but may have been pseudo-randomised by medical record number.
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not clear from the report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were reported.

Shigematsu 1973 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No pre-trial reporting plan available.
Other bias	Unclear risk	No indication of other biases

Tobin 1971

Methods	RCT with randomisation by card drawn by an individual not involved with the study. Allocation probably done in a concealed manner after randomisation. Participant, outcome assessors, and treating team all aware of allocation after trial started. No indication of power calculation. Several different tumours studied: head and neck, uterine cervix, urinary bladder, rectal, brain, and oesophagus.
Participants	• Group 1: 17 adults with carcinoma of the head and neck, 9 allocated to HBOT and 8 to control • Group 2: 14 adults with carcinoma of the uterine cervix, 7 allocated to each of HBOT and control • Group 3: 6 adults with carcinoma of the urinary bladder, 3 allocated to each of HBOT and control • Group 4: 4 adults with carcinoma of the rectum, 2 allocated to each of HBOT and control • Group 5: 4 adults with glioblastoma of the brain, 2 allocated to each of HBOT and control • Group 6: 4 adults with carcinoma of the oesophagus, 2 allocated to each of HBOT and control A further 3 participants allocated to HBOT were incomplete when trial ceased and have not been analysed.
Interventions	• Control: exact dose and fractionation schedules not given, but "normal" fractionation implies 24 to 30 fractions over 6 weeks approximately and varied with tumour site • HBOT: same regimen, conducted at 3 ATA breathing 100% oxygen, total compression time about 50 minutes
Outcomes	Death at 1 and 2 years
Notes	Trial terminated after explosive decompression of the chamber due to degradation of chamber wall from radiation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was accomplished by a drawing at random by a disinterested person of a card designating one or other of the modalities."
Allocation concealment (selection bias)	High risk	"The patient randomly assigned to receive hyperbaric oxygen was given just enough information to render an informed consent."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not clear from the report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessor

Tobin 1971 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 of 52 participants entered were excluded due to incomplete course of treatment.
Selective reporting (reporting bias)	Unclear risk	No pre-trial reporting plan available.
Other bias	Unclear risk	Trial terminated prematurely after explosive decompression of chamber.

Van Den Brenk 1968

Methods	Pseudo-RCT with allocation to group by birth date. No allocation concealment. 2 separate studies reported: one for carcinoma of the head and neck and one for carcinoma of the urinary bladder. Participant, outcome assessors, and treating team all aware of allocation. No indication of power calculation
Participants	• Trial 1: 29 adults with carcinomas of the head and neck, 17 allocated to HBOT and 12 to control • Trial 2: 16 adults with carcinoma of the urinary bladder, 8 allocated to each of HBOT and control No dropouts or losses to follow-up in either trial

Interventions	• Control:
	  * Trial 1: 3100 rads in 4 fractions
	  * Trial 2: 3300 rads in 6 fractions
	• HBOT:
	  * Trial 1: 2900 rads in 4 fractions
	  * Trial 2: 3000 rads in 6 fractions
	
	Both conducted at 3 ATA breathing 100% oxygen, total compression time about 40 minutes.

Outcomes	Death at 6 months, local tumour control early
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Allocation by birth date
Allocation concealment (selection bias)	High risk	Allocation by birth date
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No attempt to blind; HBO participants often admitted, and air participants treated as outpatients.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No attempt to blind outcome assessor

Van Den Brenk 1968 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear
Selective reporting (reporting bias)	Unclear risk	No pre-trial reporting plan available.
Other bias	High risk	Trial terminated early "because air treated patients fared worse".

Ward 1979

Methods	RCT with allocation concealment and randomisation by centrally generated envelope method. Participant, outcome assessors, and treating team all aware of allocation. No indication of power calculation
Participants	82 adults with stage IIb or III carcinoma of the uterine cervix where radiotherapy was the treatment of choice. 39 allocated to HBOT and 43 to control. 4 dropouts not analysed because treatment incomplete, plus 5 participants crossed over from HBOT to control group when they refused HBOT.
Interventions	• Control: 3150 rads external beam in 10 fractions over 2 weeks plus 3 cathetron rod placements of 950 rads each over 6 weeks • HBOT: same regimen, all external beam radiotherapy conducted at 3 ATA breathing 100% oxygen, total compression time about 30 minutes
Outcomes	Death at 1 and 5 years, local recurrence at 1 and 5 years, metastatic disease at 5 years, radiation tissue injury
Notes	See also Ward 1978, Ward 1973, and Ward 1974.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Not described but carried out by MRC statistical unit
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No evidence of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt to blind personnel or participants
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Five (participants allocated to HBO) had less than half of their fractions in HBO and were analysed as being treated in air."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All but five patients have completed four years of follow-up ..."

Ward 1979 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No pre-trial reporting plan found.
Other bias	Unclear risk	No evidence of other biases

Watson 1978

Methods	Mulitcentred RCT with allocation concealment and randomisation by centrally generated envelope method. Participant, outcome assessors, and treating team all aware of allocation at start of therapy course. No indication of power calculation
Participants	320 adults with stage III to IVa carcinoma of the uterine cervix where radiotherapy was the treatment of choice. 161 allocated to HBOT and 159 to control. No dropouts or losses to follow-up

Interventions	Different regimens of treatment were used in each of the 4 centres. Where individual centre data are given, they are used in analysis.
	• Control: (all but Group 1 had radium insertion)
	  * 1. Portsmouth: 37 participants: 3600 rads over 6 or 7 fractions in 3 weeks
	  * 2. Oxford: 34 participants: 4250 rads in 10 fractions in 4.5 weeks
	  * 3. Glasgow: 162 participants: 4500 rads in 20 fractions over 4 weeks
	  * 4. Mount Vernon: 87 participants: 5500 rads in 27 fractions over 6 weeks
	• HBOT: same regimen, with all external beam radiotherapy conducted while breathing 100% oxygen at unknown pressure and duration

Outcomes	Death at 1, 2, and 5 years, local recurrence at 5 years, metastatic disease at 1 and 5 years, late radiation tissue effects, and severe tissue reactions
Notes	See also Wiernik 1974 (referenced under Cade 1978) and Dische 1974.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"selection of treatment in hyperbaric oxygen or air was determined by opening the next in a numbered batch of envelopes supplied by the Medical Research Council's Statistical Research and Services Unit"
Allocation concealment (selection bias)	Low risk	"After admission to the trial, selection of treatment in hyperbaric oxygen or air was determined by opening the next in a numbered batch of envelopes"; supplied by the Medical Research Council's Statistical Research and Services Unit
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No evidence of any attempt to blind
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No evidence of any attempt to blind participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence of any attempt to blind for outcome assessment

Watson 1978 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants accounted for.
Selective reporting (reporting bias)	Unclear risk	No reporting plan could be assessed.
Other bias	Low risk	No evidence of other biases

ATA: atmospheres absolute
HBOT: hyperbaric oxygen therapy
MRC: Medical Research Council
rad: radiation absorbed dose
RCT: randomised controlled trial
SCC: squamous cell carcinoma

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

Study	Reason for exclusion
Bennett 1978	More fully reported in Dische 1999
Berry 1978	More fully reported in Berry 1979 and Ward 1979
Dische 1973	More fully reported in Cade 1978
Dische 1974	More fully reported in Watson 1978
Dische 1979	A summary of several trials with no new data
Dische 1991	A summary of several trials with no new data
Fletcher 1975	More fully reported in Fletcher 1977
Henk 1974	More fully reported in Henk 1977a and Henk 1986
Henk 1975	More fully reported in Henk 1977a and Henk 1986
Henk 1977b	More fully reported in Henk 1986
Kirk 1976	More fully reported in Cade 1978
Kunkler 1968	More fully reported in Henk 1977a
Lindberg 1973	More fully reported in Fletcher 1977
Mayer 2005	Review, no new data
McEwen 1968	More fully reported in Cade 1967
McEwen 1972	More fully reported in Cade 1967
MRCWP 1978	Summary of trials with no new data
Overgaard 2007	Review, no new data

Study	Reason for exclusion
Sealy 1978	More fully reported in Sealy 1986
Ward 1973	More fully reported in Ward 1979
Ward 1974	More fully reported in Ward 1979
Ward 1978	More fully reported in Ward 1979

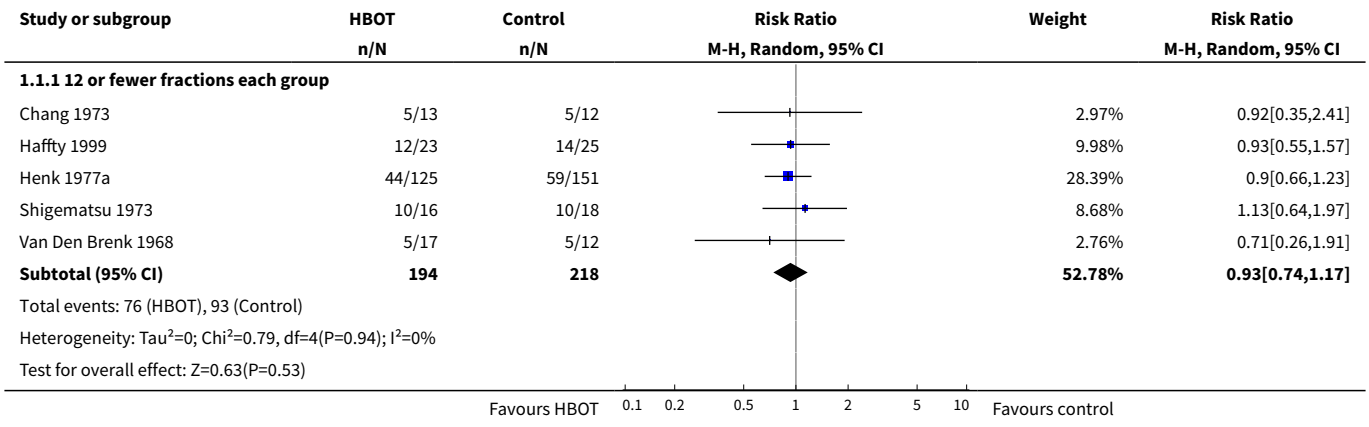
DATA AND ANALYSES

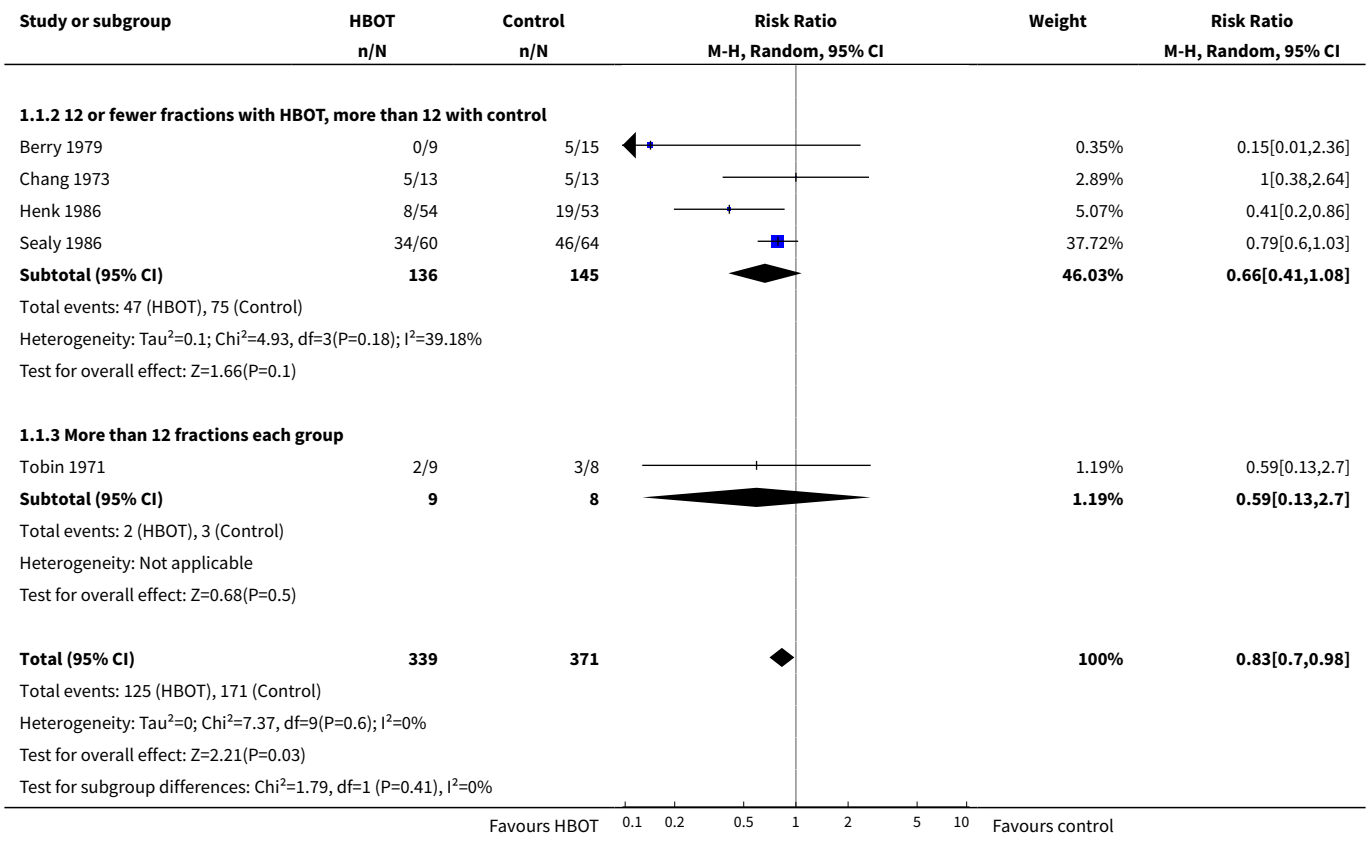
Comparison 1. Death at one year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck cancer	9	710	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
1.1 12 or fewer fractions each group	5	412	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.17]
1.2 12 or fewer fractions with HBOT, more than 12 with control	4	281	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.41, 1.08]
1.3 More than 12 fractions each group	1	17	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.13, 2.70]
2 Head and neck - best-case scenario	9	743	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.62, 0.85]
2.1 12 or fewer fractions each group	5	439	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.64, 1.02]
2.2 12 or fewer fractions with HBOT, more than 12 with control	4	287	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.43, 0.91]
2.3 More than 12 fractions each group	1	17	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.13, 2.70]
3 Head and neck - worst-case scenario	9	743	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.76, 1.15]
3.1 12 or fewer fractions each group	5	439	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.90, 1.36]
3.2 12 or fewer fractions with HBOT, more than 12 with control	4	287	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.45, 1.13]
3.3 More than 12 fractions each group	1	17	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.13, 2.70]

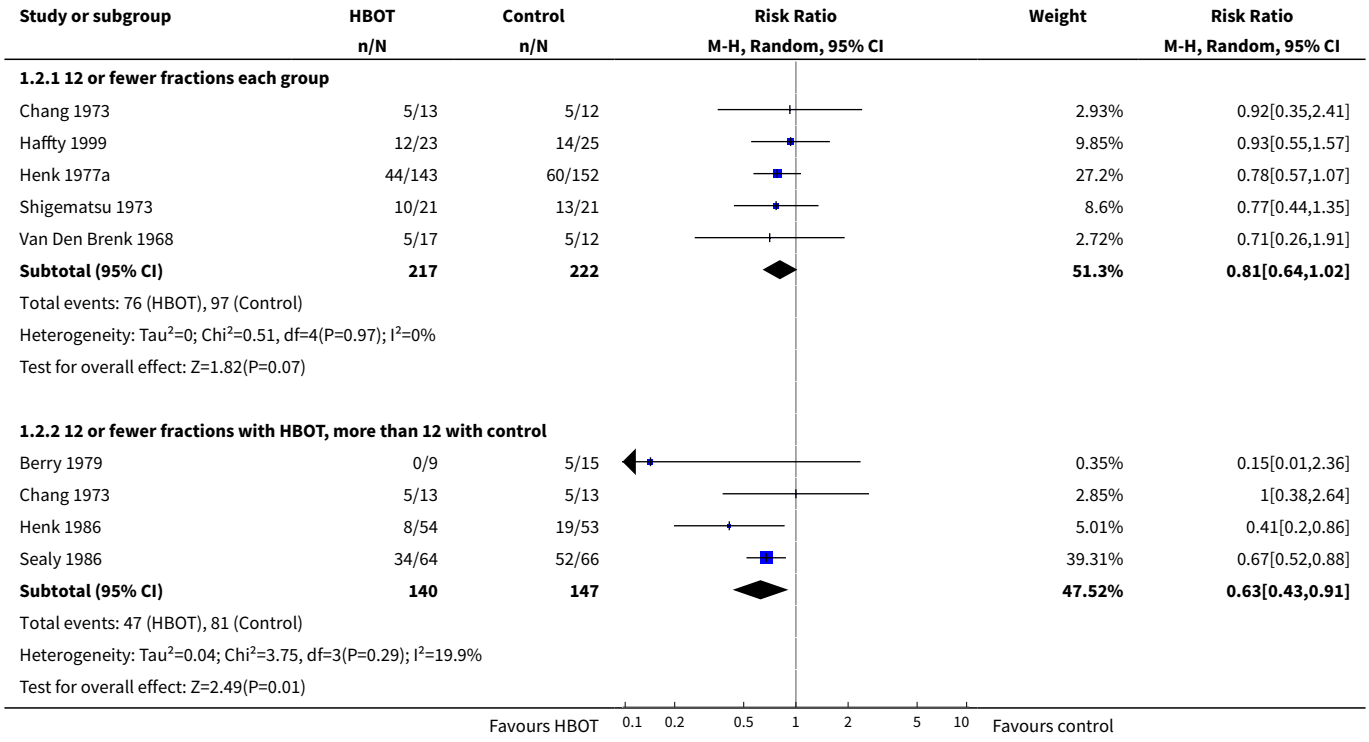
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Uterine cervix cancer	4	728	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.11]
4.1 12 or fewer fractions each groups	3	329	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.70, 1.38]
4.2 More than 12 fractions each group	3	399	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.10]
5 Uterine cervix - best-case scenario	4	732	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.69, 1.10]
6 Uterine cervix - worst-case scenario	4	732	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.15]
7 Urinary bladder cancer	4	330	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.74, 1.27]
7.1 12 or fewer fractions each group	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.35]
7.2 12 or fewer fractions with HBOT, more than 12 with control	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.44, 1.51]
7.3 More than 12 fractions each group	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.68, 3.00]
7.4 Mixed fractionation scheme	1	236	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.73, 1.44]
8 Urinary bladder - best-case scenario	4	337	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.71, 1.21]
9 Urinary bladder - worst-case scenario	4	337	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.78, 1.34]

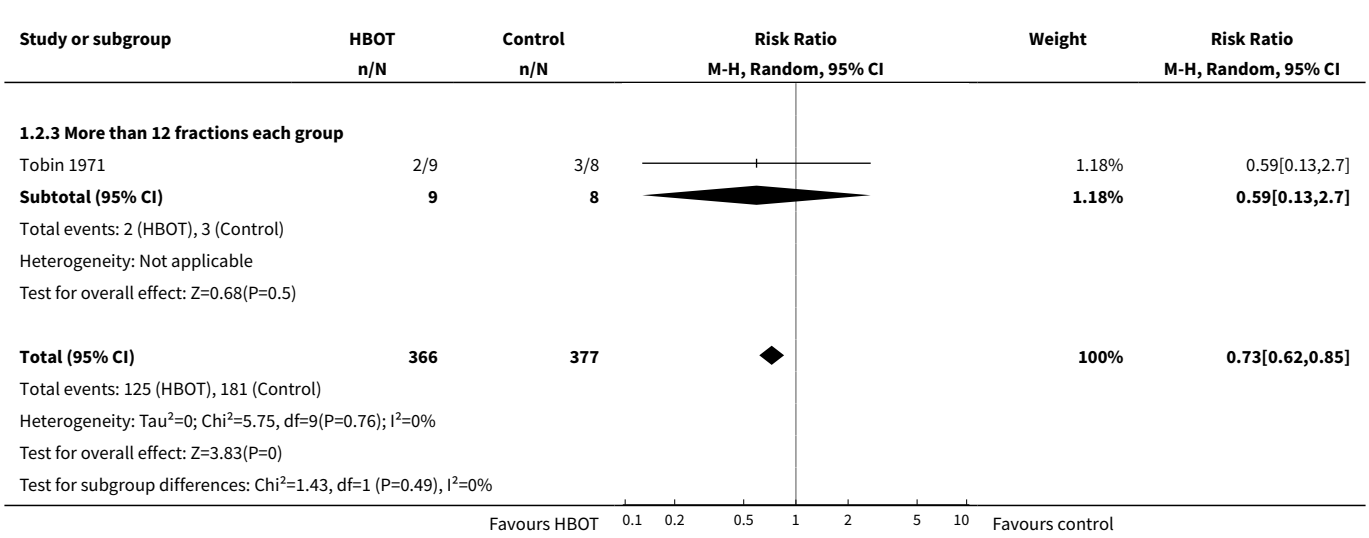
Analysis 1.1. Comparison 1 Death at one year, Outcome 1 Head and neck cancer.



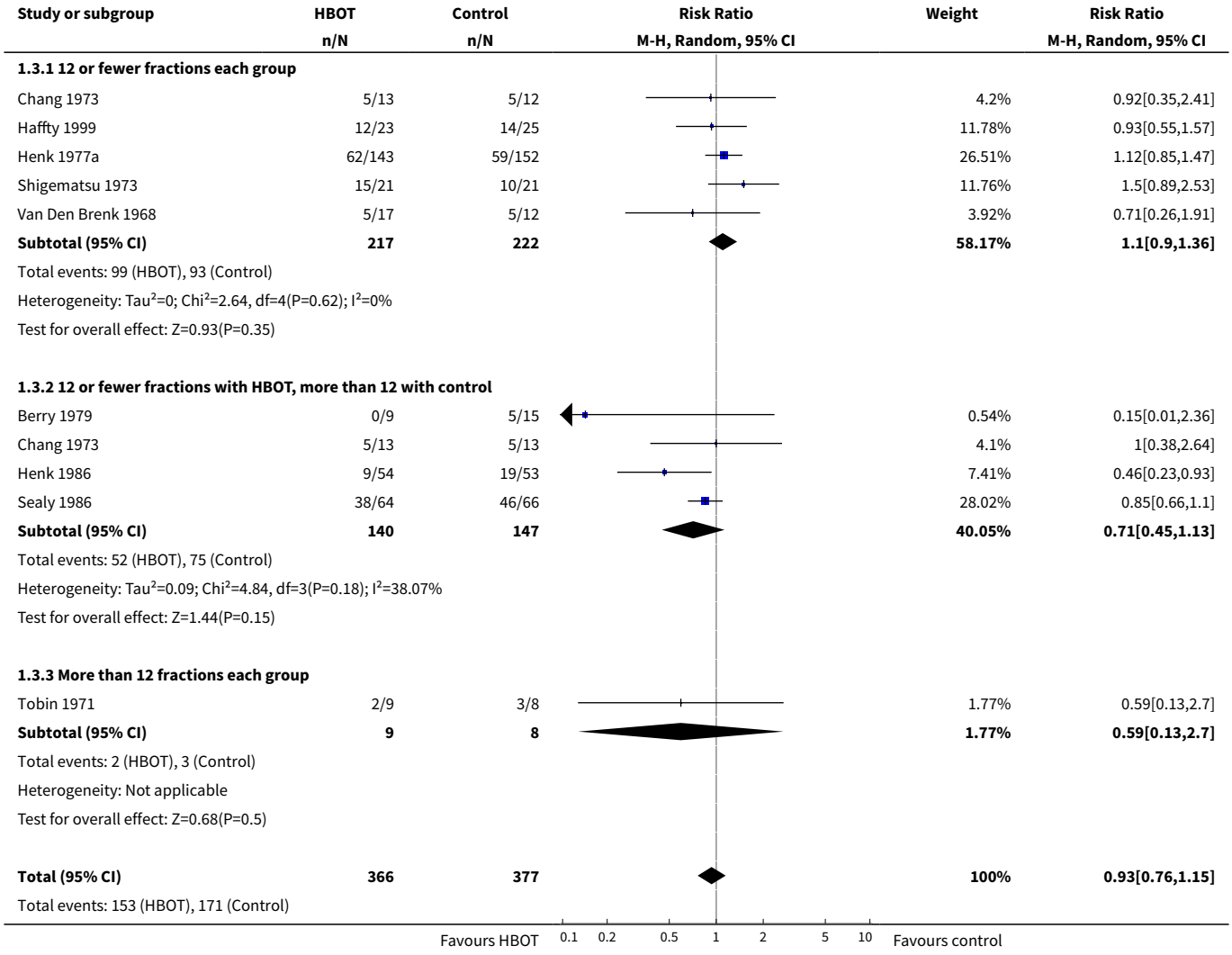


Analysis 1.2. Comparison 1 Death at one year, Outcome 2 Head and neck - best-case scenario.





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



Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.02; Chi²=11.6, df=9(P=0.24); I²=22.42%					
Test for overall effect: Z=0.66(P=0.51)					
Test for subgroup differences: Chi²=3.36, df=1 (P=0.19), I²=40.5%					

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

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 12 or fewer fractions each groups					
Dische 1999	26/92	26/88		24.81%	0.96[0.6,1.51]
Ward 1979	7/31	11/47		8.16%	0.96[0.42,2.22]
Watson 1978	13/36	12/35		11.36%	1.05[0.56,1.98]
Subtotal (95% CI)	**159**	**170**		**44.33%**	**0.98[0.7,1.38]**
Total events: 46 (Treatment), 49 (Control)					
Heterogeneity: Tau²=0; Chi²=0.06, df=2(P=0.97); I²=0%					
Test for overall effect: Z=0.1(P=0.92)					
1.4.2 More than 12 fractions each group					
Dische 1999	11/54	22/82		16.31%	0.76[0.4,1.44]
Tobin 1971	3/7	1/7		0.93%	3[0.4,22.3]
Watson 1978	31/125	41/124		38.43%	0.75[0.51,1.11]
Subtotal (95% CI)	**186**	**213**		**55.67%**	**0.79[0.57,1.1]**
Total events: 45 (Treatment), 64 (Control)					
Heterogeneity: Tau²=0; Chi²=1.78, df=2(P=0.41); I²=0%					
Test for overall effect: Z=1.4(P=0.16)					
Total (95% CI)	**345**	**383**		**100%**	**0.88[0.69,1.11]**
Total events: 91 (Treatment), 113 (Control)					
Heterogeneity: Tau²=0; Chi²=2.75, df=5(P=0.74); I²=0%					
Test for overall effect: Z=1.1(P=0.27)					
Test for subgroup differences: Chi²=0.82, df=1 (P=0.37), I²=0%					

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

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dische 1999	37/146	48/170		40.83%	0.9[0.62,1.3]
Tobin 1971	3/7	1/7		0.92%	3[0.4,22.3]
Ward 1979	7/34	12/48		9.16%	0.82[0.36,1.87]
Watson 1978	44/161	53/159		49.09%	0.82[0.59,1.15]
Total (95% CI)	**348**	**384**		**100%**	**0.87[0.69,1.1]**
Total events: 91 (HBOT), 114 (Control)					
Heterogeneity: Tau²=0; Chi²=1.63, df=3(P=0.65); I²=0%					
Test for overall effect: Z=1.14(P=0.25)					

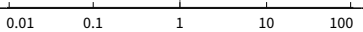
Analysis 1.6. Comparison 1 Death at one year, Outcome 6 Uterine cervix - worst-case scenario.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dische 1999	37/146	48/170		41.14%	0.9[0.62,1.3]
Tobin 1971	3/7	1/7		0.93%	3[0.4,22.3]
Ward 1979	10/34	11/48		8.46%	1.28[0.62,2.68]
Watson 1978	44/161	53/159		49.47%	0.82[0.59,1.15]
Total (95% CI)	**348**	**384**		**100%**	**0.91[0.72,1.15]**
Total events: 94 (HBOT), 113 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.58, df=3(P=0.46); I^2=0%					
Test for overall effect: Z=0.79(P=0.43)					

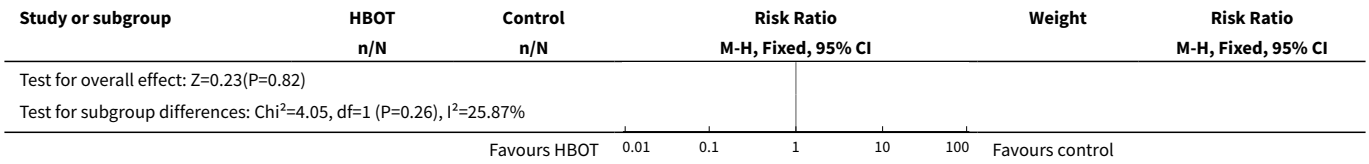
Favours HBOT — Favours control

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

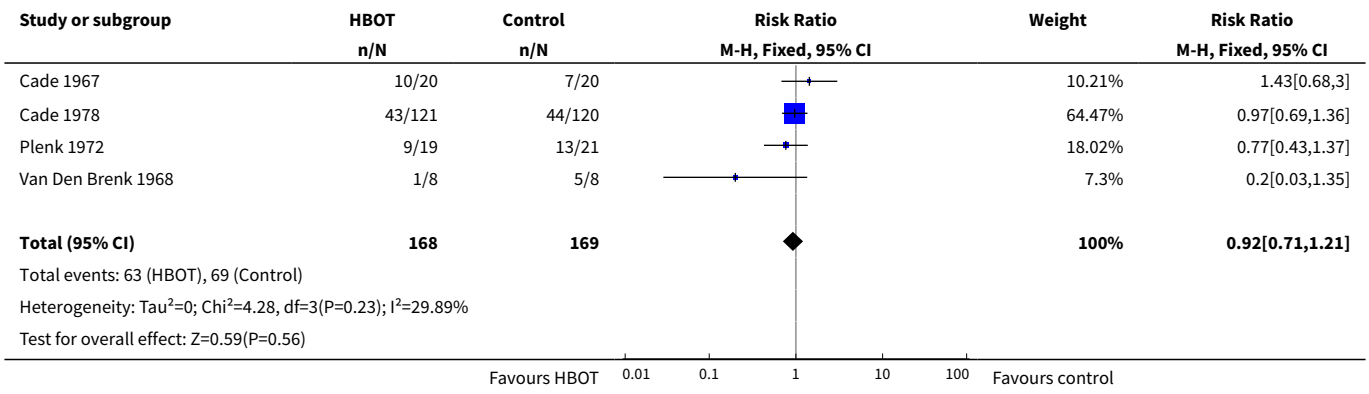
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 12 or fewer fractions each group					
Van Den Brenk 1968	1/8	5/8		7.69%	0.2[0.03,1.35]
Subtotal (95% CI)	**8**	**8**		**7.69%**	**0.2[0.03,1.35]**
Total events: 1 (HBOT), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.65(P=0.1)					
1.7.2 12 or fewer fractions with HBOT, more than 12 with control					
Plenk 1972	9/19	11/19		16.92%	0.82[0.44,1.51]
Subtotal (95% CI)	**19**	**19**		**16.92%**	**0.82[0.44,1.51]**
Total events: 9 (HBOT), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.52)					
1.7.3 More than 12 fractions each group					
Cade 1967	10/20	7/20		10.77%	1.43[0.68,3]
Subtotal (95% CI)	**20**	**20**		**10.77%**	**1.43[0.68,3]**
Total events: 10 (HBOT), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.94(P=0.35)					
1.7.4 Mixed fractionation scheme					
Cade 1978	43/118	42/118		64.62%	1.02[0.73,1.44]
Subtotal (95% CI)	**118**	**118**		**64.62%**	**1.02[0.73,1.44]**
Total events: 43 (HBOT), 42 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.14(P=0.89)					
Total (95% CI)	**165**	**165**		**100%**	**0.97[0.74,1.27]**
Total events: 63 (HBOT), 65 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.07, df=3(P=0.25); I^2=26.32%					



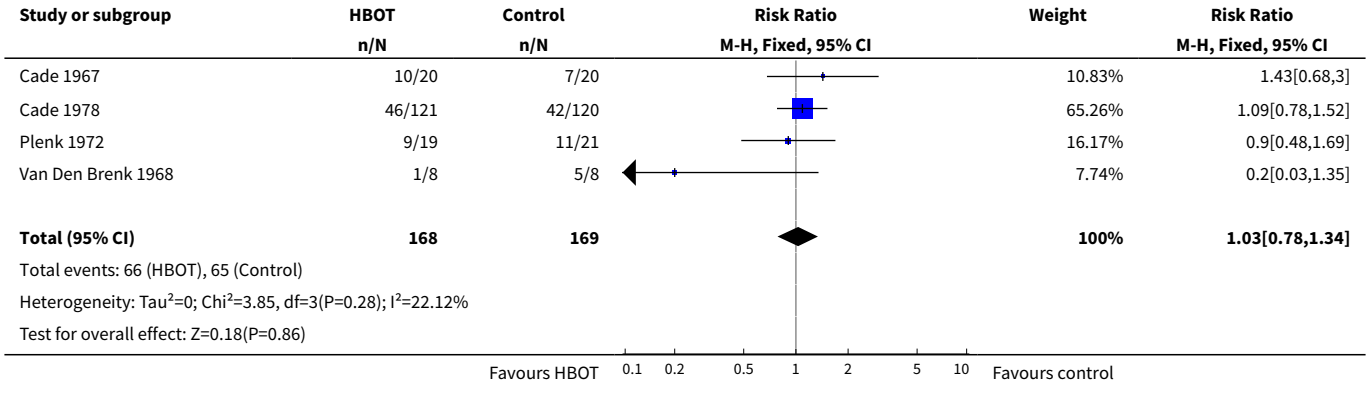
Favours HBOT — Favours control



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



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



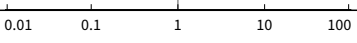
Comparison 2. Death at two years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck cancer	3	189	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.12]
1.1 12 or fewer fractions in each group	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.76, 1.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 12 or fewer fractions with HBOT, more than 12 with control	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.09]
1.3 More than 12 fractions in both HBOT and control	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.37, 3.76]
2 Head and neck - best-case scenario	3	195	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.79, 1.07]
2.1 12 or fewer fractions in each group	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.76, 1.40]
2.2 12 or fewer fractions with HBOT, more than 12 with control	1	130	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.73, 1.03]
2.3 More than 12 fractions in both HBOT and control	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.37, 3.76]
3 Head and neck - worst-case scenario	3	195	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.15]
3.1 12 or fewer fractions in each group	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.76, 1.40]
3.2 12 or fewer fractions with HBOT, more than 12 with control	1	130	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.14]
3.3 More than 12 fractions in both HBOT and control	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.37, 3.76]
4 Uterine cervix cancer	4	607	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.76, 1.15]
4.1 12 or fewer fractions in HBOT and control	1	71	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.47, 1.09]
4.2 More than 12 fractions in HBOT and control	4	536	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.81, 1.21]
5 Urinary bladder carcinoma	2	24	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.63, 3.92]
6 Urinary bladder - best-case	2	58	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.04, 5.24]
7 Urinary bladder - worst-case	2	58	Risk Ratio (M-H, Fixed, 95% CI)	5.18 [2.18, 12.31]

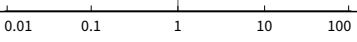
Analysis 2.1. Comparison 2 Death at two years, Outcome 1 Head and neck cancer.

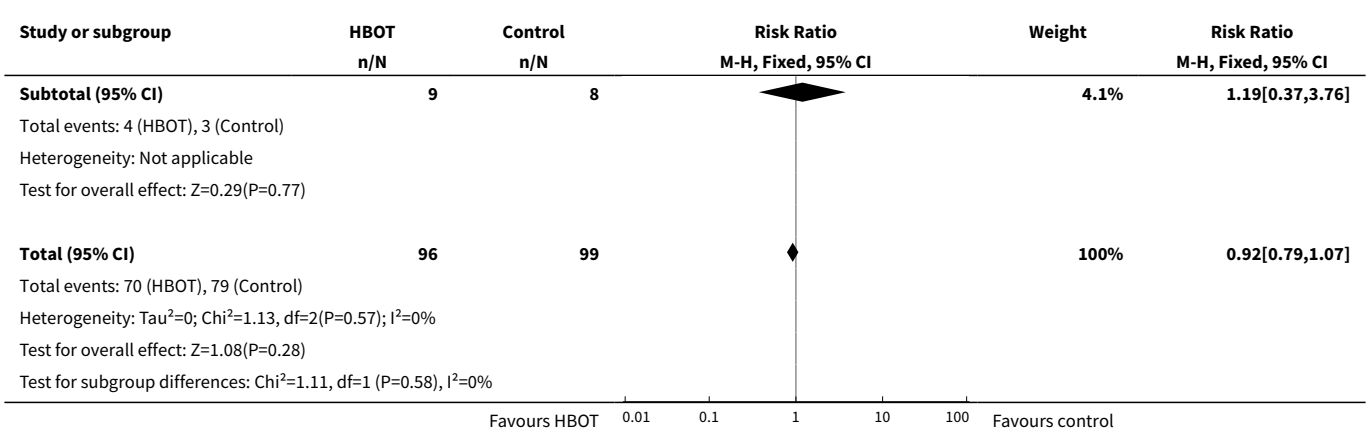
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 12 or fewer fractions in each group					
Haffty 1999	18/23	19/25		24.4%	1.03[0.76,1.4]
Subtotal (95% CI)	**23**	**25**		**24.4%**	**1.03[0.76,1.4]**
Total events: 18 (Treatment), 19 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.19(P=0.85)					
2.1.2 12 or fewer fractions with HBOT, more than 12 with control					
Sealy 1986	48/60	55/64		71.34%	0.93[0.79,1.09]
Subtotal (95% CI)	**60**	**64**		**71.34%**	**0.93[0.79,1.09]**
Total events: 48 (Treatment), 55 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.87(P=0.38)					
2.1.3 More than 12 fractions in both HBOT and control					
Tobin 1971	4/9	3/8		4.26%	1.19[0.37,3.76]
Subtotal (95% CI)	**9**	**8**		**4.26%**	**1.19[0.37,3.76]**
Total events: 4 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.29(P=0.77)					
Total (95% CI)	**92**	**97**		**100%**	**0.97[0.83,1.12]**
Total events: 70 (Treatment), 77 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.49, df=2(P=0.78); I^2=0%					
Test for overall effect: Z=0.46(P=0.64)					
Test for subgroup differences: Chi^2=0.46, df=1 (P=0.79), I^2=0%					



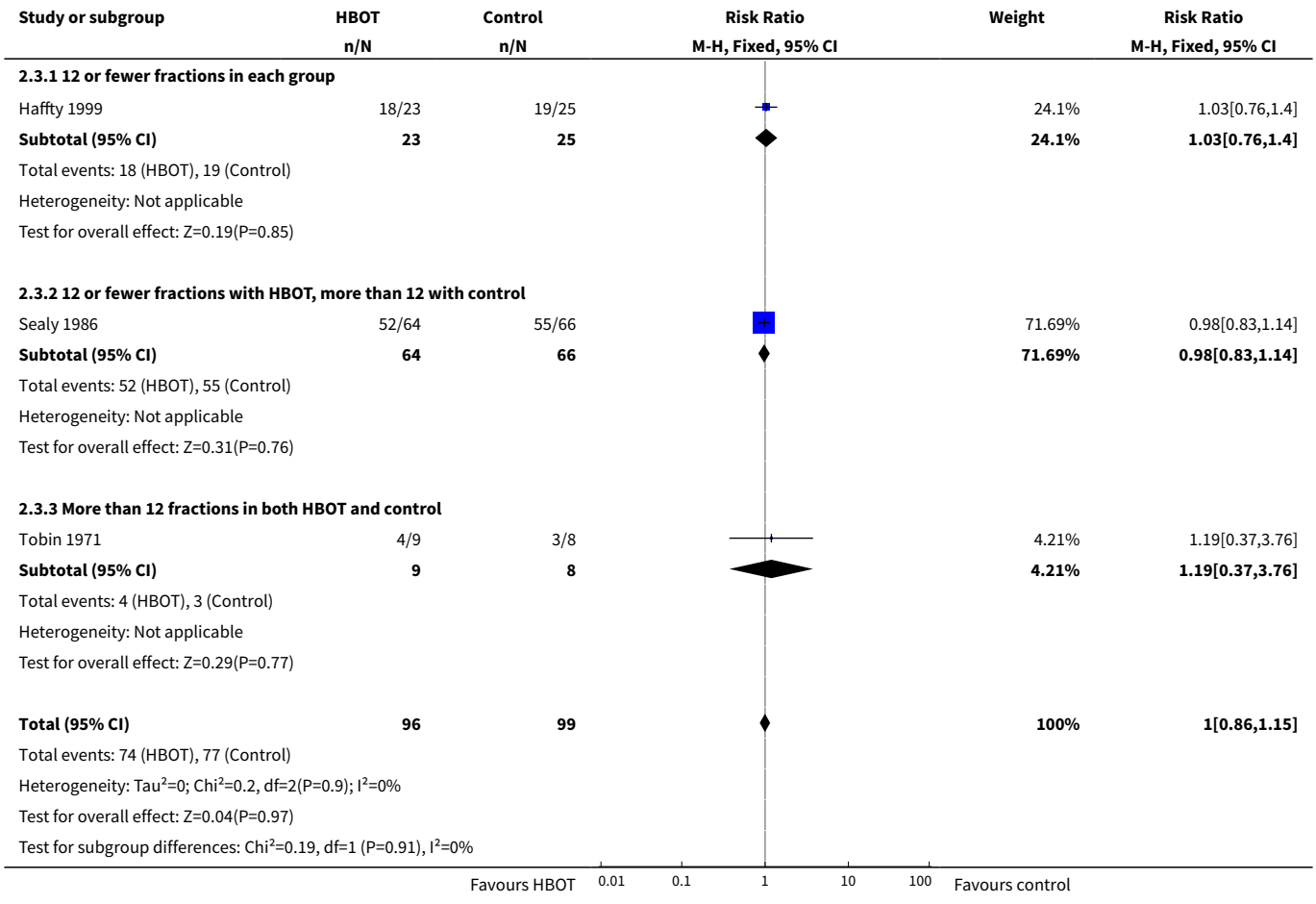
Analysis 2.2. Comparison 2 Death at two years, Outcome 2 Head and neck - best-case scenario.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 12 or fewer fractions in each group					
Haffty 1999	18/23	19/25		23.49%	1.03[0.76,1.4]
Subtotal (95% CI)	**23**	**25**		**23.49%**	**1.03[0.76,1.4]**
Total events: 18 (HBOT), 19 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.19(P=0.85)					
2.2.2 12 or fewer fractions with HBOT, more than 12 with control					
Sealy 1986	48/64	57/66		72.41%	0.87[0.73,1.03]
Subtotal (95% CI)	**64**	**66**		**72.41%**	**0.87[0.73,1.03]**
Total events: 48 (HBOT), 57 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.62(P=0.11)					
2.2.3 More than 12 fractions in both HBOT and control					
Tobin 1971	4/9	3/8		4.1%	1.19[0.37,3.76]

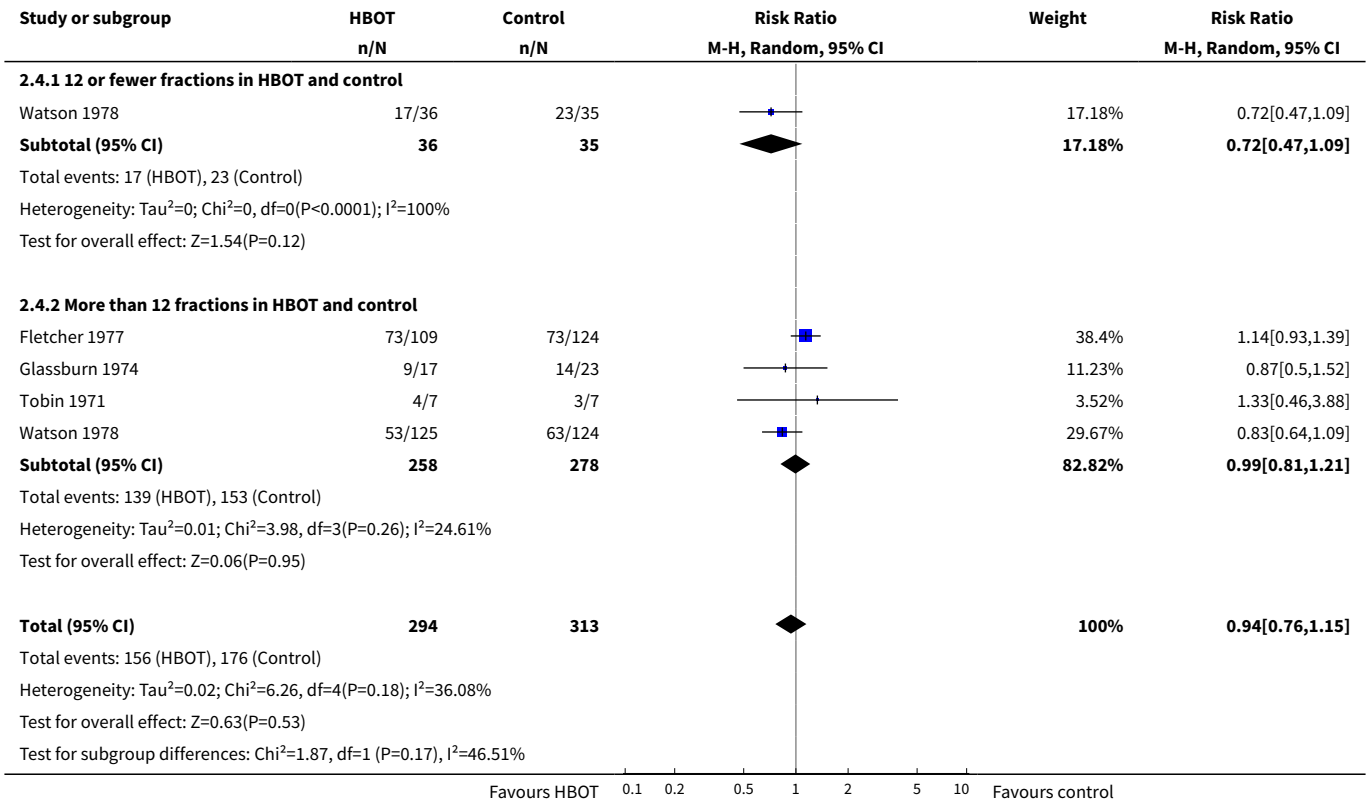




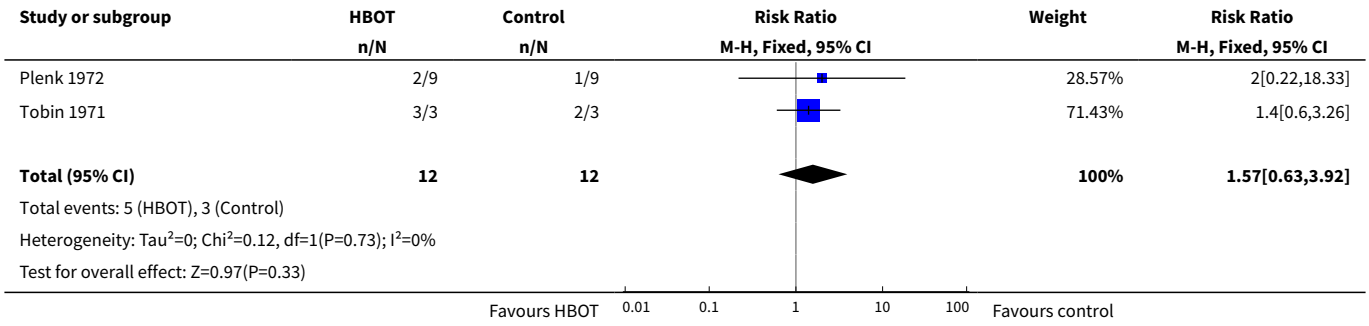
Analysis 2.3. Comparison 2 Death at two years, Outcome 3 Head and neck - worst-case scenario.



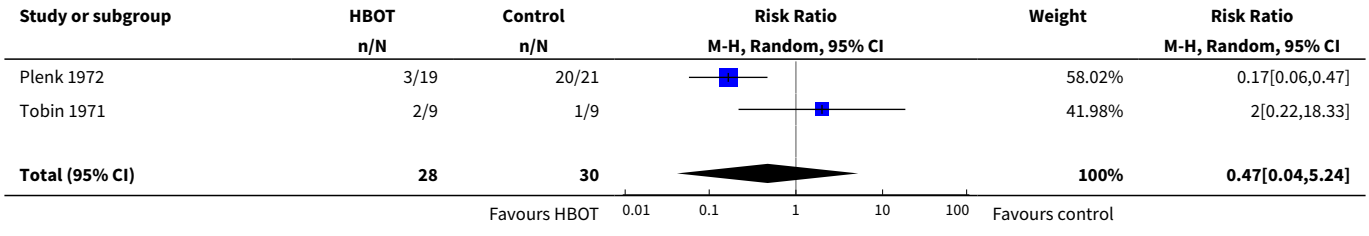
Analysis 2.4. Comparison 2 Death at two years, Outcome 4 Uterine cervix cancer.

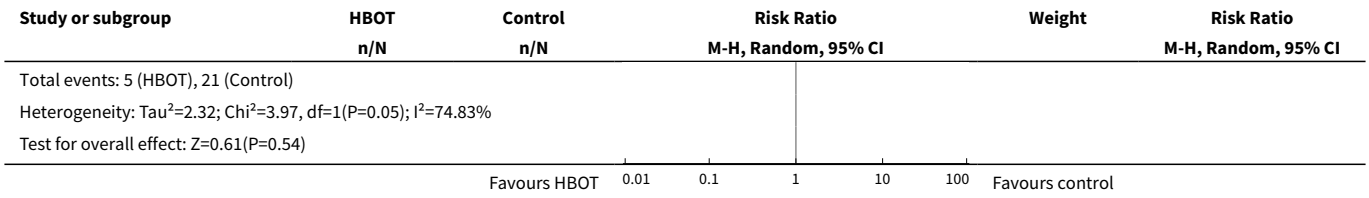


Analysis 2.5. Comparison 2 Death at two years, Outcome 5 Urinary bladder carcinoma.

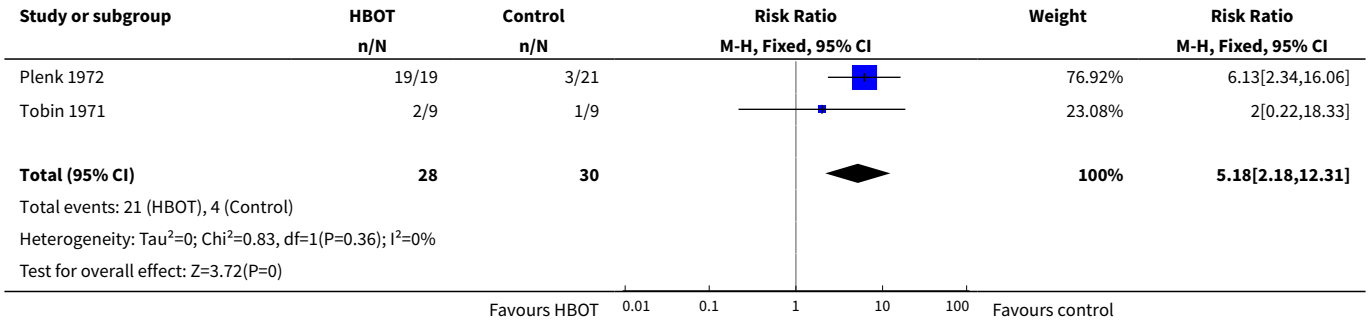


Analysis 2.6. Comparison 2 Death at two years, Outcome 6 Urinary bladder - best-case.





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



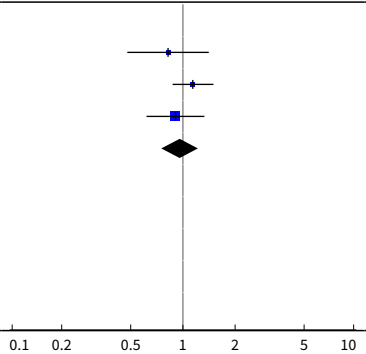
Comparison 3. Death at five years

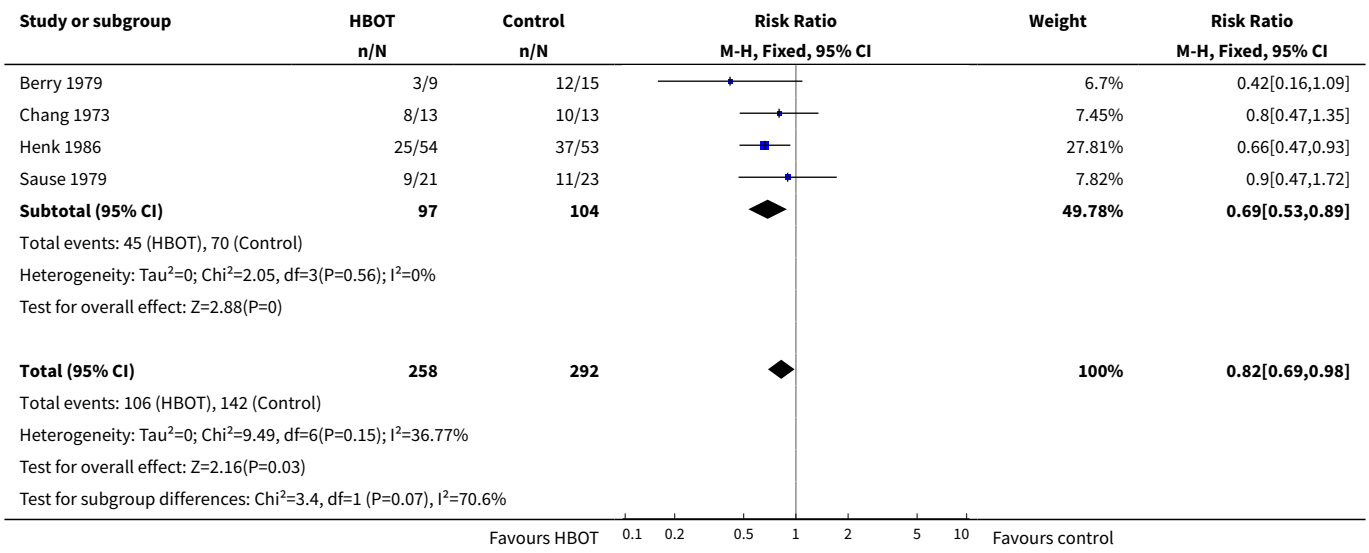
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck cancer	6	550	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.69, 0.98]
1.1 12 or fewer fractions each group	3	349	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.75, 1.22]
1.2 12 or fewer fractions in HBOT, more than 12 in control	4	201	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.53, 0.89]
2 Head and neck - best-case scenario	6	575	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.64, 0.92]
2.1 12 or fewer fractions in each group	3	368	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.12]
2.2 12 or fewer fractions in HBOT, more than 12 in control	4	207	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.51, 0.85]
3 Head and neck - worst-case scenario	6	575	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.81, 1.13]
3.1 12 or fewer fractions each group	3	368	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.92, 1.45]
3.2 12 or fewer fractions in HBOT, more than 12 in control	4	207	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.59, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Uterine cervix cancer	4	772	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.14]
4.1 12 or fewer fractions each group	3	329	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.62, 1.34]
4.2 More than 12 fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.15]
4.3 12 or fewer fractions in HBOT versus more than 12 in control	1	58	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.70, 1.61]
5 Uterine cancer - best-case scenario	4	783	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.09]
5.1 12 or fewer fractions in each group	3	333	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.61, 1.28]
5.2 More than 12 fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.15]
5.3 12 or fewer fractions in HBOT versus more than 12 in control	1	65	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.57, 1.32]
6 Uterine cancer - worst-case scenario	4	783	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.81, 1.18]
6.1 12 or fewer fractions in each group	3	333	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.63, 1.38]
6.2 More than 12 fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.15]
6.3 12 or fewer fractions in HBOT versus more than 12 in control	1	65	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.79, 1.77]

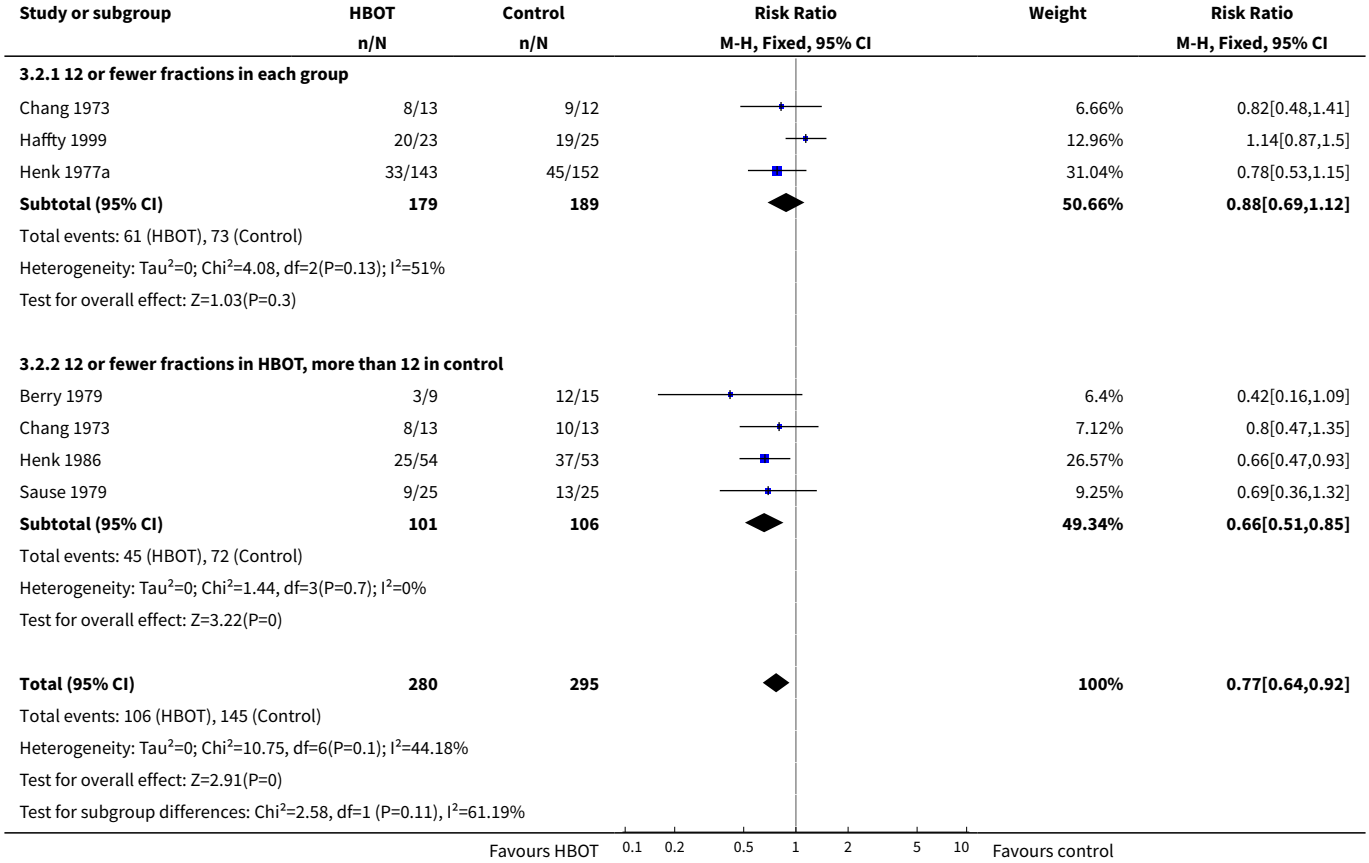
Analysis 3.1. Comparison 3 Death at five years, Outcome 1 Head and neck cancer.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 12 or fewer fractions each group					
Chang 1973	8/13	9/12		6.97%	0.82[0.48,1.41]
Haffty 1999	20/23	19/25		13.56%	1.14[0.87,1.5]
Henk 1977a	33/125	44/151		29.68%	0.91[0.62,1.33]
Subtotal (95% CI)	**161**	**188**		**50.22%**	**0.96[0.75,1.22]**
Total events: 61 (HBOT), 72 (Control)					
Heterogeneity: Tau²=0; Chi²=2.04, df=2(P=0.36); I²=1.89%					
Test for overall effect: Z=0.34(P=0.73)					
3.1.2 12 or fewer fractions in HBOT, more than 12 in control					





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

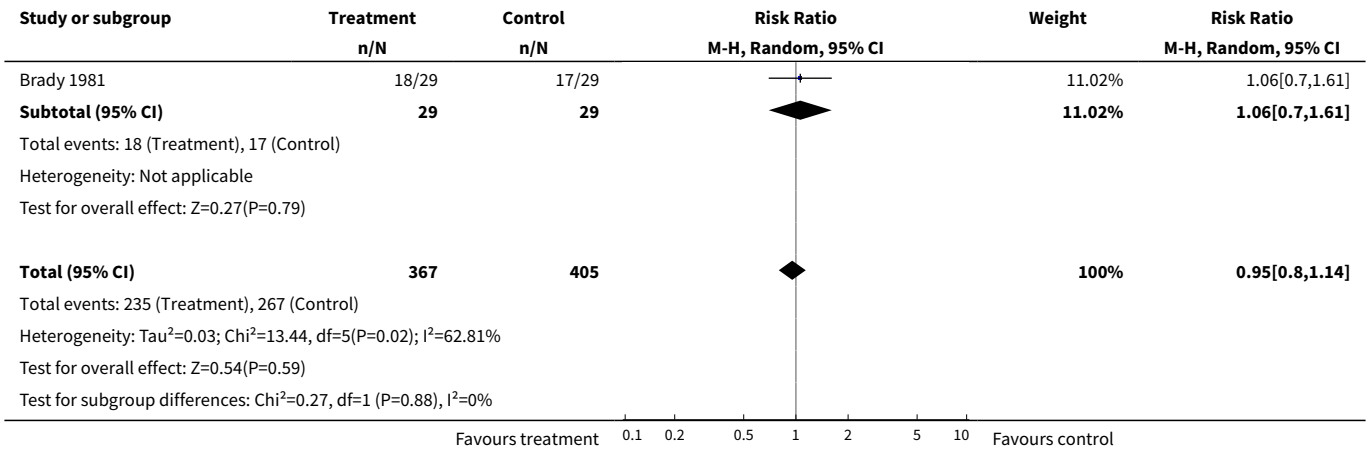


Analysis 3.3. Comparison 3 Death at five years, Outcome 3 Head and neck - worst-case scenario.

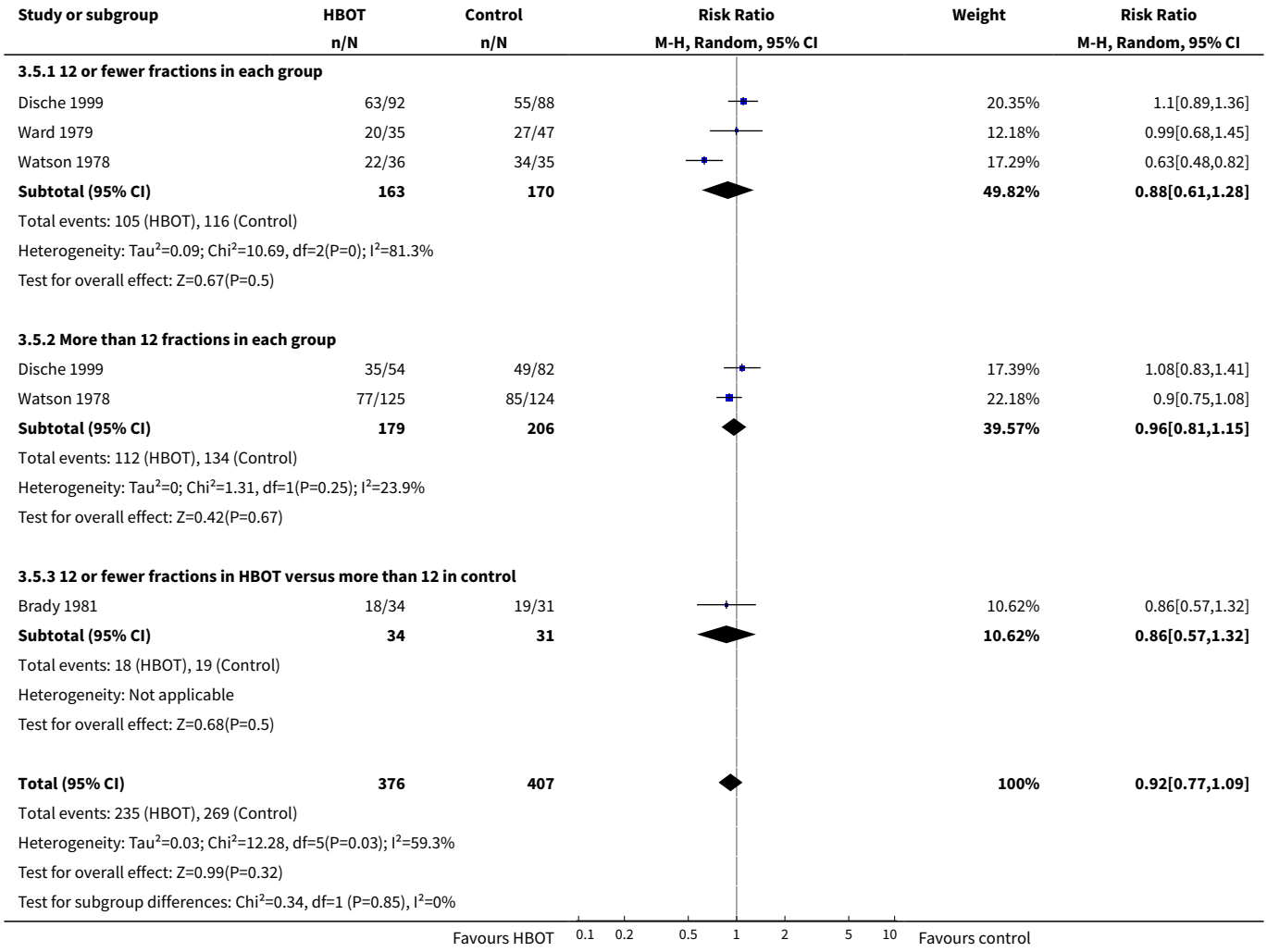
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 12 or fewer fractions each group					
Chang 1973	8/13	9/12		6.8%	0.82[0.48,1.41]
Haffty 1999	20/23	19/25		13.24%	1.14[0.87,1.5]
Henk 1977a	51/143	44/152		31.01%	1.23[0.88,1.72]
Subtotal (95% CI)	**179**	**189**		**51.05%**	**1.15[0.92,1.45]**
Total events: 79 (HBOT), 72 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.69, df=2(P=0.43); I^2=0%					
Test for overall effect: Z=1.23(P=0.22)					
3.3.2 12 or fewer fractions in HBOT, more than 12 in control					
Berry 1979	3/9	12/15		6.54%	0.42[0.16,1.09]
Chang 1973	8/13	10/13		7.27%	0.8[0.47,1.35]
Henk 1986	26/54	37/53		27.15%	0.69[0.5,0.96]
Sause 1979	13/25	11/25		8%	1.18[0.66,2.11]
Subtotal (95% CI)	**101**	**106**		**48.95%**	**0.75[0.59,0.96]**
Total events: 50 (HBOT), 70 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.11, df=3(P=0.25); I^2=26.99%					
Test for overall effect: Z=2.3(P=0.02)					
Total (95% CI)	**280**	**295**		**100%**	**0.96[0.81,1.13]**
Total events: 129 (HBOT), 142 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.87, df=6(P=0.06); I^2=49.45%					
Test for overall effect: Z=0.52(P=0.6)					
Test for subgroup differences: Chi^2=6.36, df=1 (P=0.01), I^2=84.28%					

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

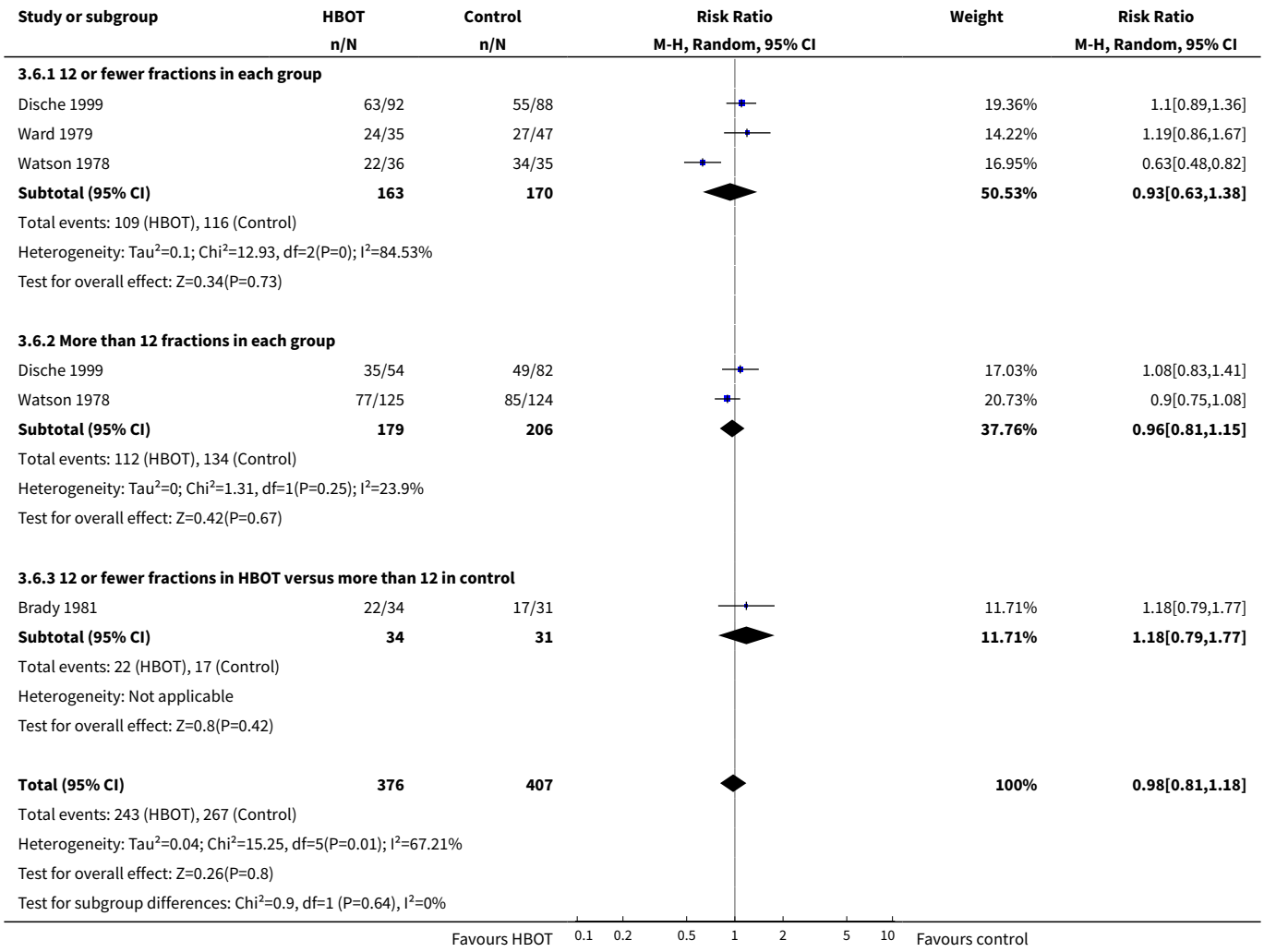
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 12 or fewer fractions each group					
Dische 1999	63/92	55/88		19.92%	1.1[0.89,1.36]
Ward 1979	20/31	27/47		13.1%	1.12[0.78,1.61]
Watson 1978	22/36	34/35		17.16%	0.63[0.48,0.82]
Subtotal (95% CI)	**159**	**170**		**50.18%**	**0.91[0.62,1.34]**
Total events: 105 (Treatment), 116 (Control)					
Heterogeneity: Tau^2=0.1; Chi^2=11.82, df=2(P=0); I^2=83.09%					
Test for overall effect: Z=0.46(P=0.65)					
3.4.2 More than 12 fractions in each group					
Dische 1999	35/54	49/82		17.25%	1.08[0.83,1.41]
Watson 1978	77/125	85/124		21.55%	0.9[0.75,1.08]
Subtotal (95% CI)	**179**	**206**		**38.8%**	**0.96[0.81,1.15]**
Total events: 112 (Treatment), 134 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.31, df=1(P=0.25); I^2=23.9%					
Test for overall effect: Z=0.42(P=0.67)					
3.4.3 12 or fewer fractions in HBOT versus more than 12 in control					



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



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



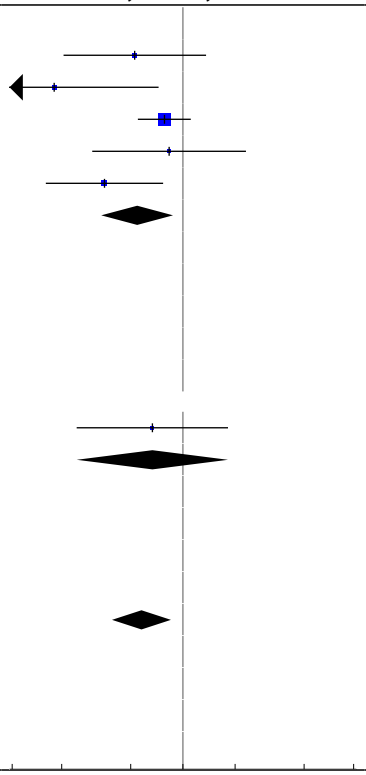
Comparison 4. Failure to control local tumour at three months

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Fewer than 12 fractions in HBOT versus more than 12 in control	1	26	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.24, 1.82]
3 Head and neck - worst-case scenario	5	465	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.35, 1.00]
3.1 12 or fewer fractions in each group	5	439	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.30, 1.05]
3.2 Fewer than 12 fractions in HBOT versus more than 12 in control	1	26	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.24, 1.82]

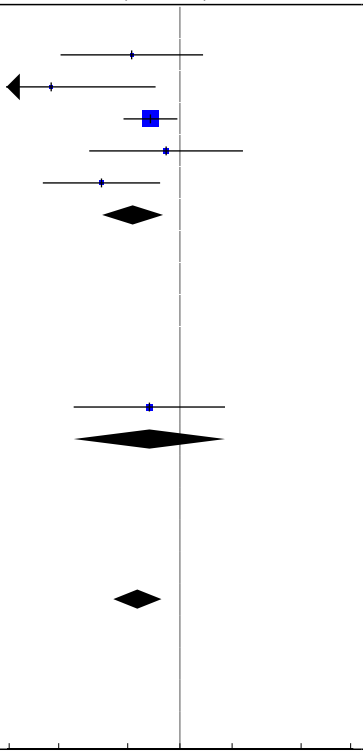
Analysis 4.1. Comparison 4 Failure to control local tumour at three months, Outcome 1 Head and neck cancer.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 12 or fewer fractions each group					
Chang 1973	4/13	7/12		13.14%	0.53[0.2,1.36]
Haffty 1999	2/23	12/25		6.98%	0.18[0.05,0.72]
Henk 1977a	35/125	54/151		38.82%	0.78[0.55,1.11]
Shigematsu 1973	5/21	6/21		11.65%	0.83[0.3,2.31]
Van Den Brenk 1968	5/17	10/12		17.46%	0.35[0.16,0.77]
Subtotal (95% CI)	**199**	**221**		**88.05%**	**0.54[0.34,0.88]**
Total events: 51 (HBOT), 89 (Control)					
Heterogeneity: Tau^2=0.12; Chi^2=7.13, df=4(P=0.13); I^2=43.9%					
Test for overall effect: Z=2.5(P=0.01)					
4.1.2 Fewer than 12 fractions in HBOT group versus more than 12 in control					
Chang 1973	4/13	6/13		11.95%	0.67[0.24,1.82]
Subtotal (95% CI)	**13**	**13**		**11.95%**	**0.67[0.24,1.82]**
Total events: 4 (HBOT), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.79(P=0.43)					
Total (95% CI)	**212**	**234**		**100%**	**0.58[0.39,0.85]**
Total events: 55 (HBOT), 95 (Control)					
Heterogeneity: Tau^2=0.07; Chi^2=7.14, df=5(P=0.21); I^2=29.92%					
Test for overall effect: Z=2.76(P=0.01)					
Test for subgroup differences: Chi^2=0.13, df=1 (P=0.72), I^2=0%					



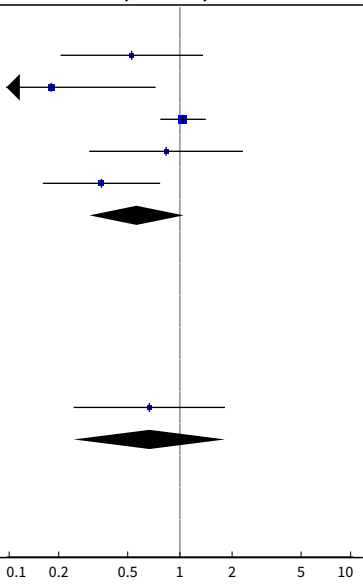
Analysis 4.2. Comparison 4 Failure to control local tumour at three months, Outcome 2 Head and neck cancer - best-case scenario.

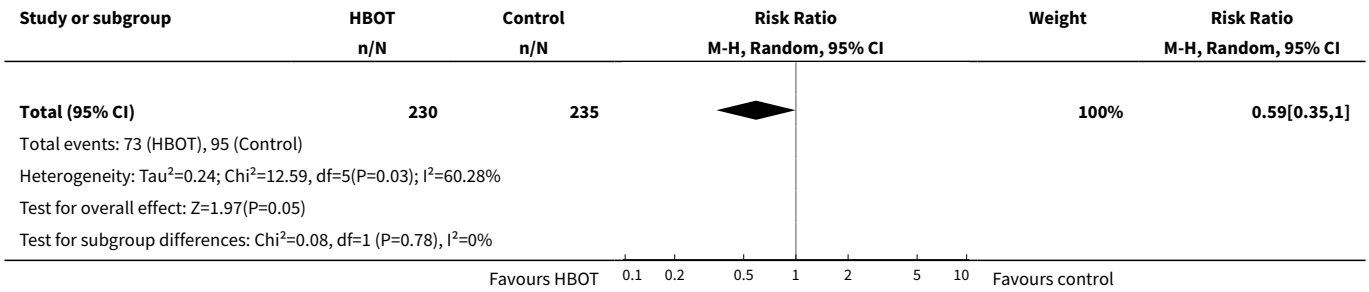
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 12 or fewer fractions in each group					
Chang 1973	4/13	7/12		10.59%	0.53[0.2,1.36]
Haffty 1999	2/23	12/25		5.14%	0.18[0.05,0.72]
Henk 1977a	35/143	55/152		50.6%	0.68[0.47,0.97]
Shigematsu 1973	5/21	6/21		9.17%	0.83[0.3,2.31]
Van Den Brenk 1968	5/17	10/12		15.05%	0.35[0.16,0.77]
Subtotal (95% CI)	**217**	**222**		**90.55%**	**0.53[0.36,0.8]**
Total events: 51 (HBOT), 90 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=5.53, df=4(P=0.24); I^2=27.63%					
Test for overall effect: Z=3.04(P=0)					
4.2.2 Fewer than 12 fractions in HBOT versus more than 12 in control					
Chang 1973	4/13	6/13		9.45%	0.67[0.24,1.82]
Subtotal (95% CI)	**13**	**13**		**9.45%**	**0.67[0.24,1.82]**
Total events: 4 (HBOT), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.79(P=0.43)					
Total (95% CI)	**230**	**235**		**100%**	**0.57[0.41,0.78]**
Total events: 55 (HBOT), 96 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=5.59, df=5(P=0.35); I^2=10.63%					
Test for overall effect: Z=3.46(P=0)					
Test for subgroup differences: Chi^2=0.16, df=1 (P=0.69), I^2=0%					



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

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 12 or fewer fractions in each group					
Chang 1973	4/13	7/12		15.39%	0.53[0.2,1.36]
Haffty 1999	2/23	12/25		9.8%	0.18[0.05,0.72]
Henk 1977a	53/143	54/152		27.81%	1.04[0.77,1.41]
Shigematsu 1973	5/21	6/21		14.21%	0.83[0.3,2.31]
Van Den Brenk 1968	5/17	10/12		18.32%	0.35[0.16,0.77]
Subtotal (95% CI)	**217**	**222**		**85.54%**	**0.56[0.3,1.05]**
Total events: 69 (HBOT), 89 (Control)					
Heterogeneity: Tau^2=0.32; Chi^2=12.44, df=4(P=0.01); I^2=67.86%					
Test for overall effect: Z=1.8(P=0.07)					
4.3.2 Fewer than 12 fractions in HBOT versus more than 12 in control					
Chang 1973	4/13	6/13		14.46%	0.67[0.24,1.82]
Subtotal (95% CI)	**13**	**13**		**14.46%**	**0.67[0.24,1.82]**
Total events: 4 (HBOT), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.79(P=0.43)					



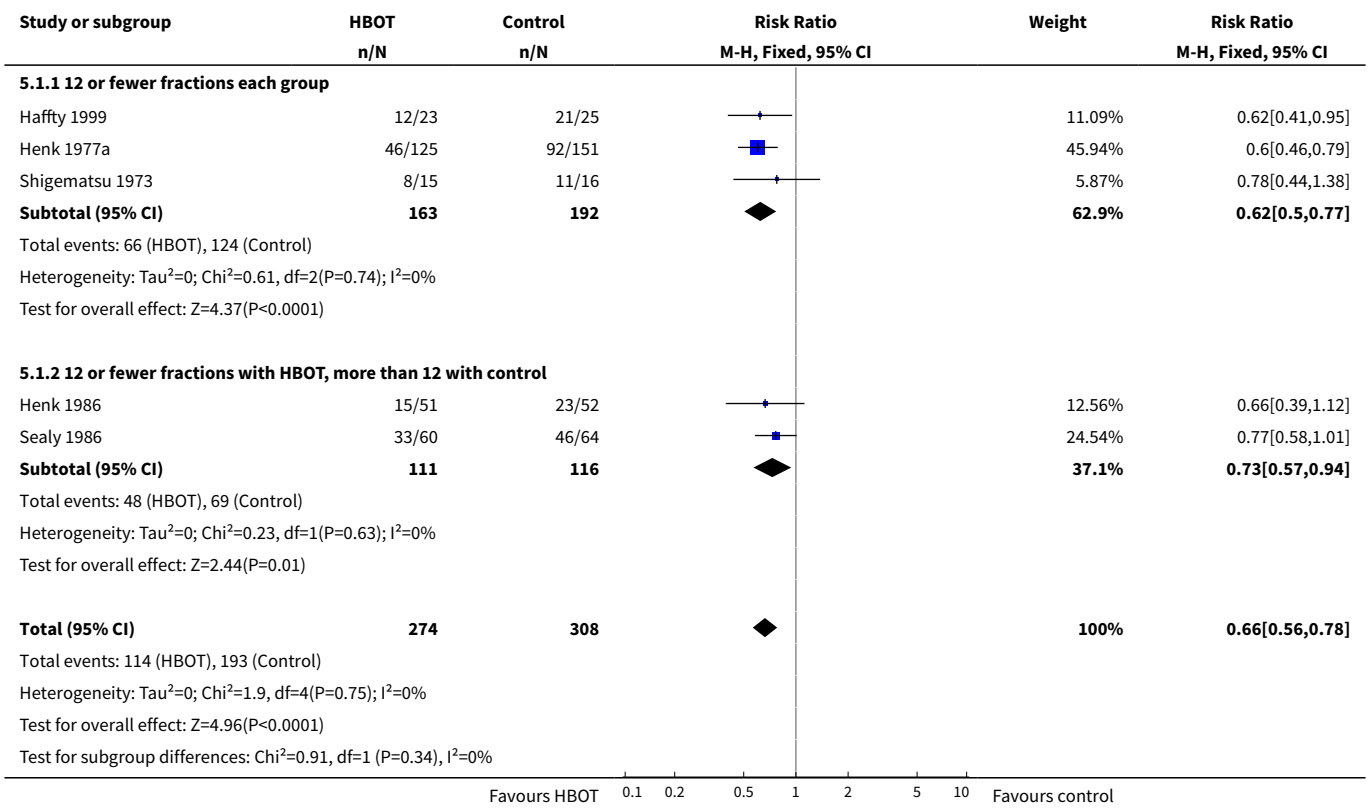


Comparison 5. Local recurrence at one year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck cancer	5	582	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.56, 0.78]
1.1 12 or fewer fractions each group	3	355	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.50, 0.77]
1.2 12 or fewer fractions with HBOT, more than 12 with control	2	227	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.94]
2 Head and neck cancer - best-case scenario	5	611	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.51, 0.71]
2.1 12 or fewer fractions in each group	3	374	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.45, 0.70]
2.2 12 or fewer fractions with HBOT, more than 12 with control	2	237	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.53, 0.87]
3 Head and neck cancer - worst-case scenario	5	611	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.65, 0.87]
3.1 12 or fewer fractions in each group	3	374	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.60, 0.87]
3.2 12 or fewer fractions with HBOT, more than 12 with control	2	237	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.64, 1.03]
4 Uterine cervix cancer	3	714	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.63, 1.06]
4.1 12 or fewer fractions each group	3	329	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.57, 1.27]
4.2 More than 12 fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.28]
5 Uterine cervix cancer - best-case scenario	3	718	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.63, 1.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 12 or fewer fractions in each group	3	333	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.58, 1.17]
5.2 More than 12 fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.28]
6 Uterine cervix cancer - worst-case scenario	3	718	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.63, 1.19]
6.1 12 or fewer fractions in each group	3	333	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.56, 1.58]
6.2 More than 12 fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.28]

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

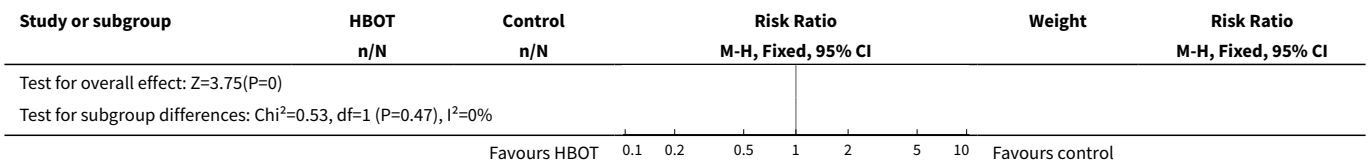


Analysis 5.2. Comparison 5 Local recurrence at one year, Outcome 2 Head and neck cancer - best-case scenario.

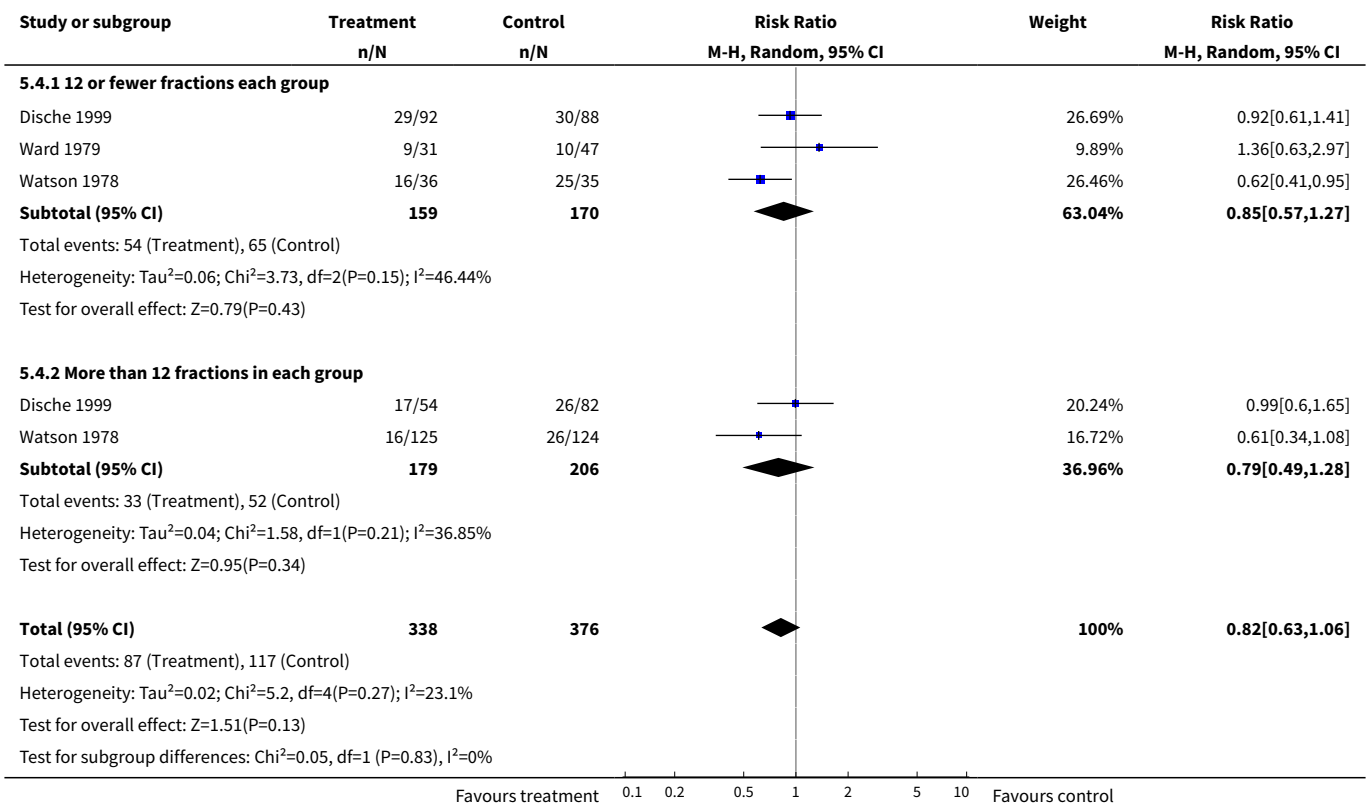
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 12 or fewer fractions in each group					
Haffty 1999	12/23	21/25		10.46%	0.62[0.41,0.95]
Henk 1977a	46/143	93/152		46.86%	0.53[0.4,0.69]
Shigematsu 1973	8/15	11/16		5.53%	0.78[0.44,1.38]
Subtotal (95% CI)	**181**	**193**		**62.85%**	**0.56[0.45,0.7]**
Total events: 66 (HBOT), 125 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.63, df=2(P=0.44); I^2=0%					
Test for overall effect: Z=5.19(P<0.0001)					
5.2.2 12 or fewer fractions with HBOT, more than 12 with control					
Henk 1986	15/54	24/53		12.59%	0.61[0.36,1.03]
Sealy 1986	33/64	48/66		24.56%	0.71[0.54,0.94]
Subtotal (95% CI)	**118**	**119**		**37.15%**	**0.68[0.53,0.87]**
Total events: 48 (HBOT), 72 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.24, df=1(P=0.62); I^2=0%					
Test for overall effect: Z=3.02(P=0)					
Total (95% CI)	**299**	**312**		**100%**	**0.61[0.51,0.71]**
Total events: 114 (HBOT), 197 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3, df=4(P=0.56); I^2=0%					
Test for overall effect: Z=5.97(P<0.0001)					
Test for subgroup differences: Chi^2=1.15, df=1 (P=0.28), I^2=13.42%					

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

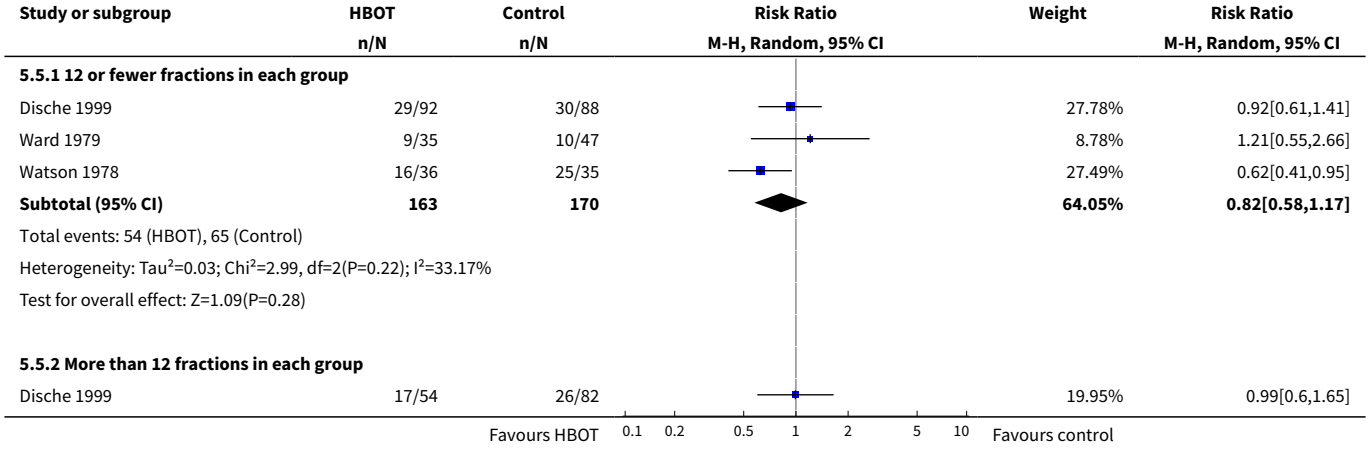
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.3.1 12 or fewer fractions in each group					
Haffty 1999	12/23	21/25		10.68%	0.62[0.41,0.95]
Henk 1977a	64/143	92/152		47.32%	0.74[0.59,0.92]
Shigematsu 1973	8/15	11/16		5.65%	0.78[0.44,1.38]
Subtotal (95% CI)	**181**	**193**		**63.65%**	**0.72[0.6,0.87]**
Total events: 84 (HBOT), 124 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.58, df=2(P=0.75); I^2=0%					
Test for overall effect: Z=3.39(P=0)					
5.3.2 12 or fewer fractions with HBOT, more than 12 with control					
Henk 1986	18/54	23/53		12.32%	0.77[0.47,1.25]
Sealy 1986	37/64	46/66		24.03%	0.83[0.64,1.08]
Subtotal (95% CI)	**118**	**119**		**36.35%**	**0.81[0.64,1.03]**
Total events: 55 (HBOT), 69 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.78); I^2=0%					
Test for overall effect: Z=1.75(P=0.08)					
Total (95% CI)	**299**	**312**		**100%**	**0.75[0.65,0.87]**
Total events: 139 (HBOT), 193 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.34, df=4(P=0.85); I^2=0%					

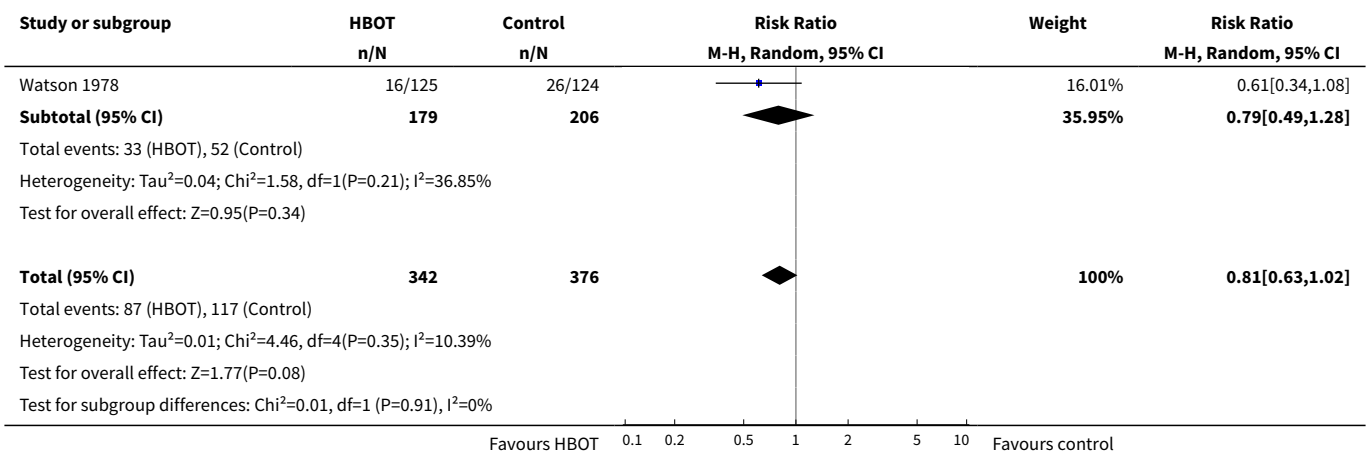


Analysis 5.4. Comparison 5 Local recurrence at one year, Outcome 4 Uterine cervix cancer.

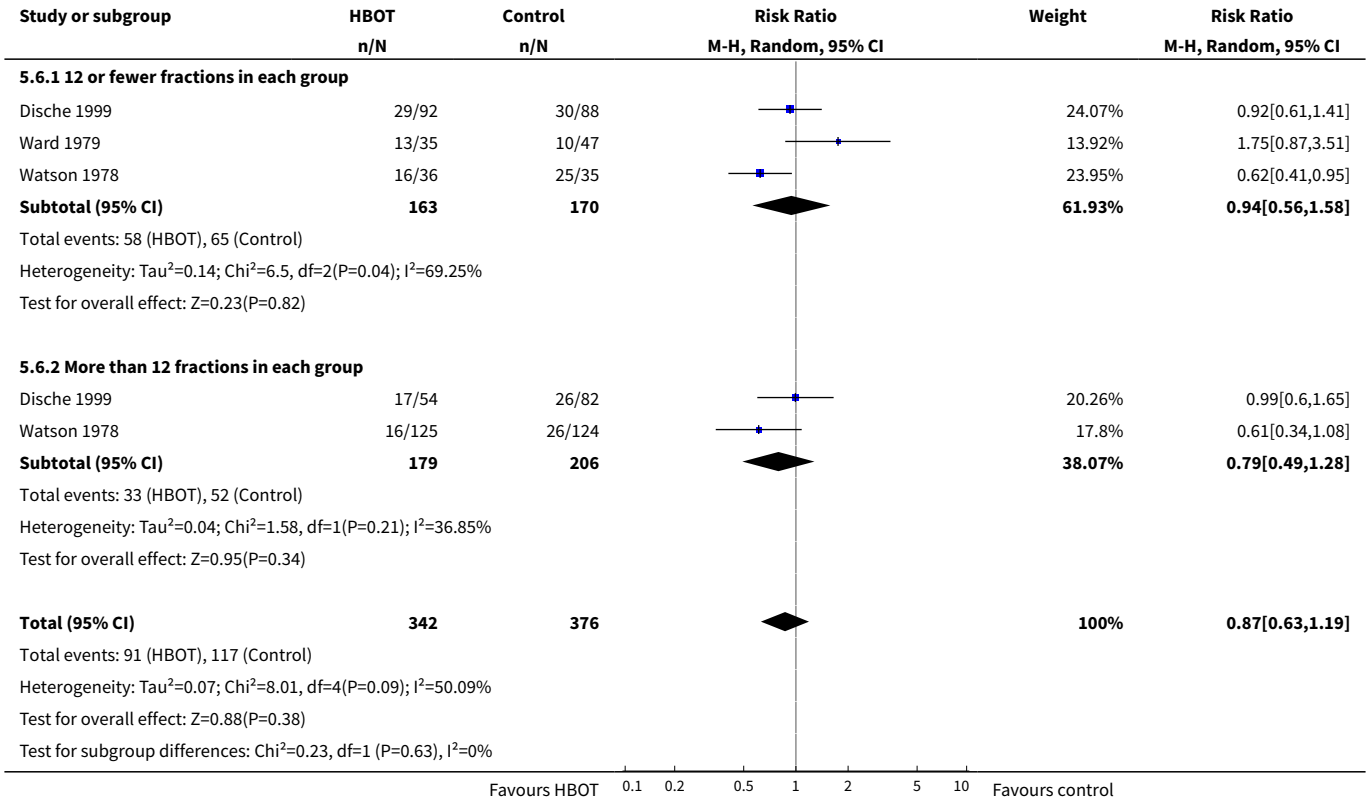


Analysis 5.5. Comparison 5 Local recurrence at one year, Outcome 5 Uterine cervix cancer - best-case scenario.





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

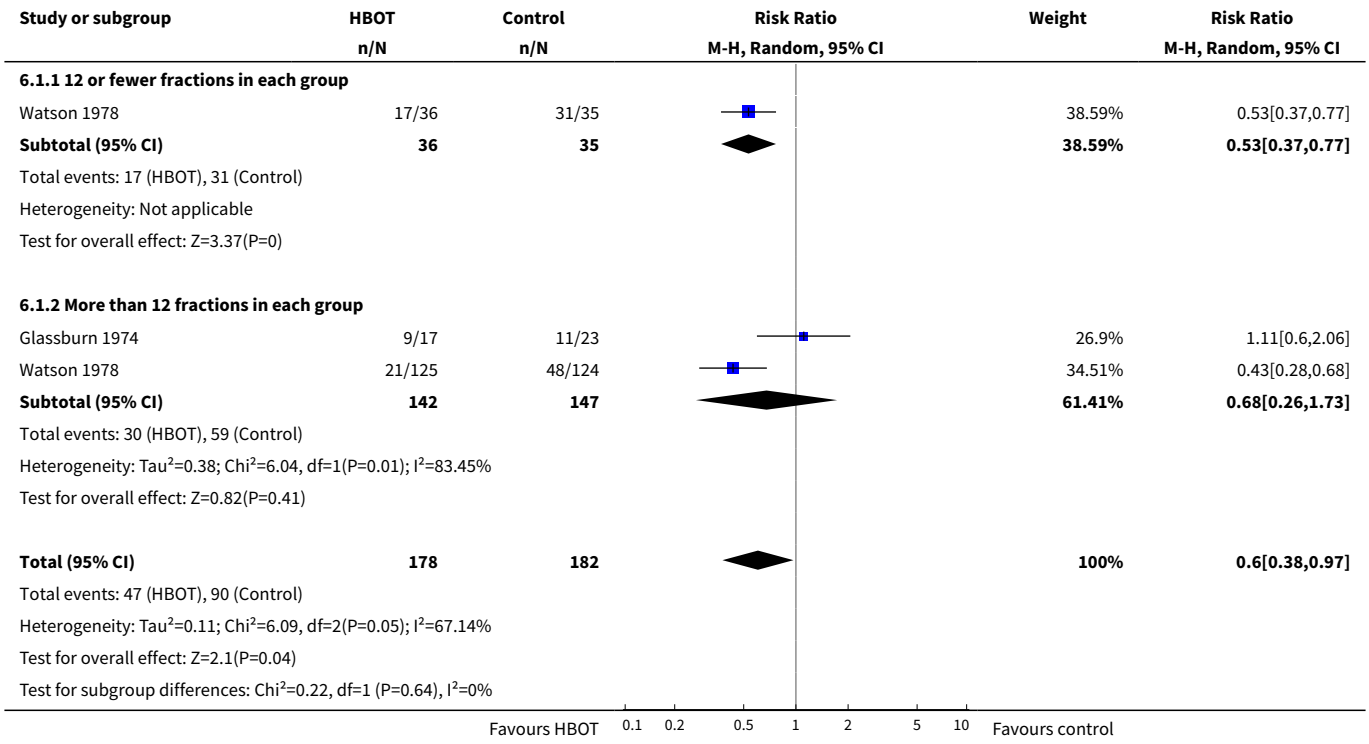


Comparison 6. Local recurrence at two years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Uterine cervix cancer	2	360	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.38, 0.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 12 or fewer fractions in each group	1	71	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.37, 0.77]
1.2 More than 12 fractions in each group	2	289	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.26, 1.73]

Analysis 6.1. Comparison 6 Local recurrence at two years, Outcome 1 Uterine cervix cancer.



Comparison 7. Local recurrence at five years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck cancer	5	495	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.62, 0.95]
1.1 12 or fewer fractions in each group	2	324	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.88]
1.2 12 or fewer fractions in HBOT, more than 12 in control	3	171	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.39, 1.43]
2 Head and neck cancer - best-case scenario	5	521	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.57, 0.86]

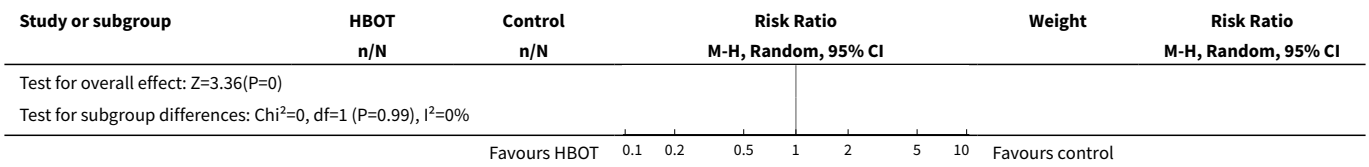
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 12 or fewer fractions in each group	2	343	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.52, 0.94]
2.2 12 or fewer fractions in HBOT, more than 12 in control	3	178	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.43, 1.12]
3 Head and neck cancer - worst-case scenario	5	521	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.66, 1.06]
3.1 12 or fewer fractions in each group	2	343	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.69, 0.95]
3.2 12 or fewer fractions in HBOT, more than 12 in control	3	178	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.38, 1.71]
4 Uterine cervix cancer	4	772	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.65, 1.13]
4.1 12 or fewer fractions each group	3	329	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.49, 1.41]
4.2 12 or fewer fractions in HBOT group versus more than 12 fractions in control	1	58	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.58, 2.71]
4.3 12 or more fractions in each group	2	385	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.32]
5 Uterine cervix cancer - best-case scenario	4	783	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.97]
5.1 12 or fewer fractions in each group	3	333	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.70, 1.05]
5.2 12 or fewer fractions in HBOT, more than 12 in controls	2	385	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 1.01]
5.3 More than 12 fractions in each group	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.44, 1.89]
6 Uterine cervix cancer - worst-case scenario	4	783	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.76, 1.03]
6.1 12 or fewer fractions in each group	3	333	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.10]
6.2 12 or fewer fractions in HBOT, more than 12 in controls	2	385	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 1.01]
6.3 More than 12 fractions in each group	1	65	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.78, 3.28]

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

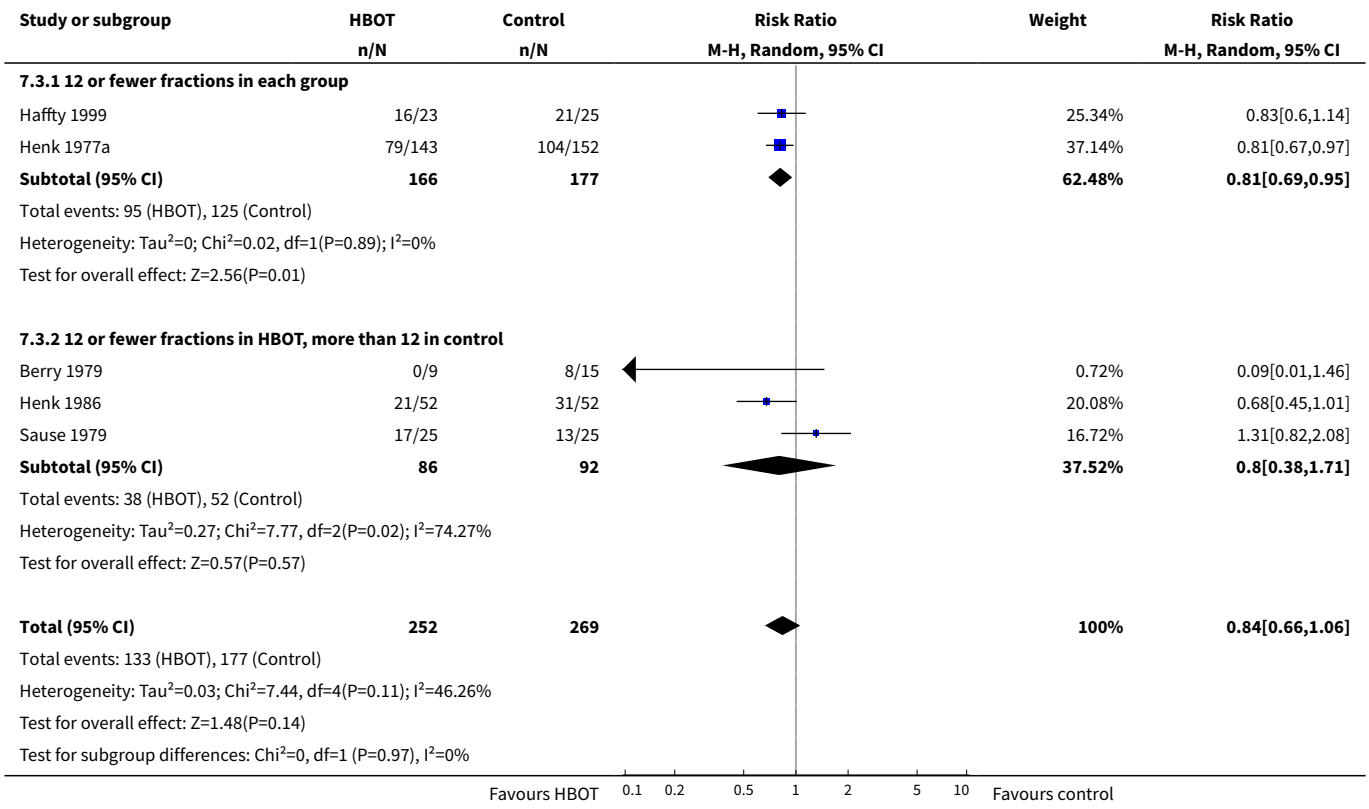
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 12 or fewer fractions in each group					
Haffty 1999	16/23	21/25		26.18%	0.83[0.6,1.14]
Henk 1977a	61/125	104/151		39.7%	0.71[0.57,0.87]
Subtotal (95% CI)	**148**	**176**		**65.88%**	**0.74[0.62,0.88]**
Total events: 77 (HBOT), 125 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.68, df=1(P=0.41); I^2=0%					
Test for overall effect: Z=3.33(P=0)					
7.1.2 12 or fewer fractions in HBOT, more than 12 in control					
Berry 1979	0/9	8/15		0.59%	0.09[0.01,1.46]
Henk 1986	20/51	31/52		19.04%	0.66[0.44,0.99]
Sause 1979	13/21	13/23		14.49%	1.1[0.67,1.79]
Subtotal (95% CI)	**81**	**90**		**34.12%**	**0.75[0.39,1.43]**
Total events: 33 (HBOT), 52 (Control)					
Heterogeneity: Tau^2=0.18; Chi^2=5.44, df=2(P=0.07); I^2=63.24%					
Test for overall effect: Z=0.87(P=0.38)					
Total (95% CI)	**229**	**266**		**100%**	**0.77[0.62,0.95]**
Total events: 110 (HBOT), 177 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=5.9, df=4(P=0.21); I^2=32.2%					
Test for overall effect: Z=2.46(P=0.01)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.97), I^2=0%					

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

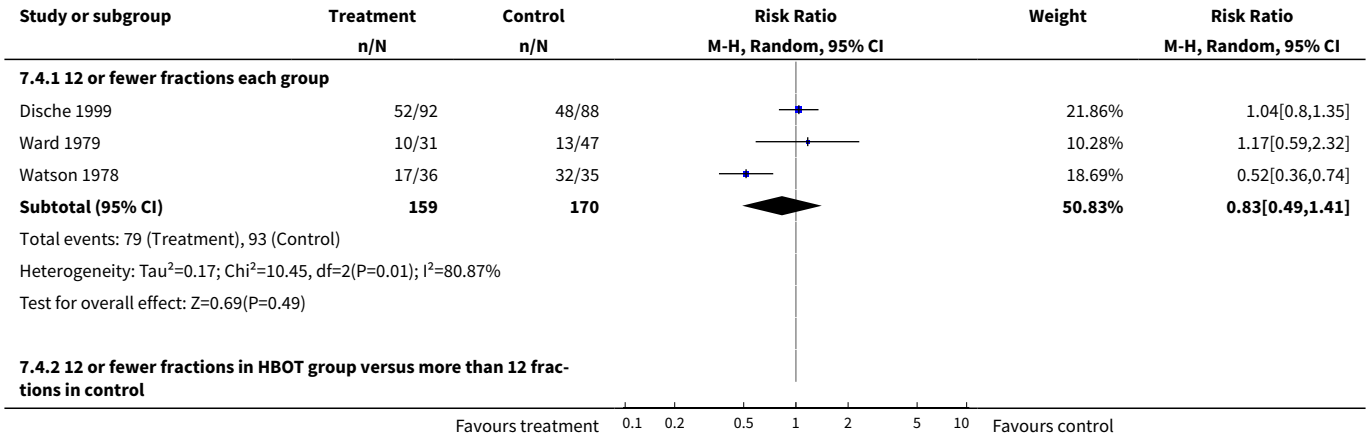
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.2.1 12 or fewer fractions in each group					
Haffty 1999	16/23	21/25		26.51%	0.83[0.6,1.14]
Henk 1977a	61/143	105/152		39.73%	0.62[0.5,0.77]
Subtotal (95% CI)	**166**	**177**		**66.23%**	**0.7[0.52,0.94]**
Total events: 77 (HBOT), 126 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=2.38, df=1(P=0.12); I^2=58.02%					
Test for overall effect: Z=2.38(P=0.02)					
7.2.2 12 or fewer fractions in HBOT, more than 12 in control					
Berry 1979	0/9	8/15		0.58%	0.09[0.01,1.46]
Henk 1986	20/52	31/52		18.94%	0.65[0.43,0.97]
Sause 1979	13/25	15/25		14.25%	0.87[0.53,1.42]
Subtotal (95% CI)	**86**	**92**		**33.77%**	**0.7[0.43,1.12]**
Total events: 33 (HBOT), 54 (Control)					
Heterogeneity: Tau^2=0.07; Chi^2=3.33, df=2(P=0.19); I^2=39.92%					
Test for overall effect: Z=1.49(P=0.14)					
Total (95% CI)	**252**	**269**		**100%**	**0.7[0.57,0.86]**
Total events: 110 (HBOT), 180 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=5.67, df=4(P=0.23); I^2=29.41%					

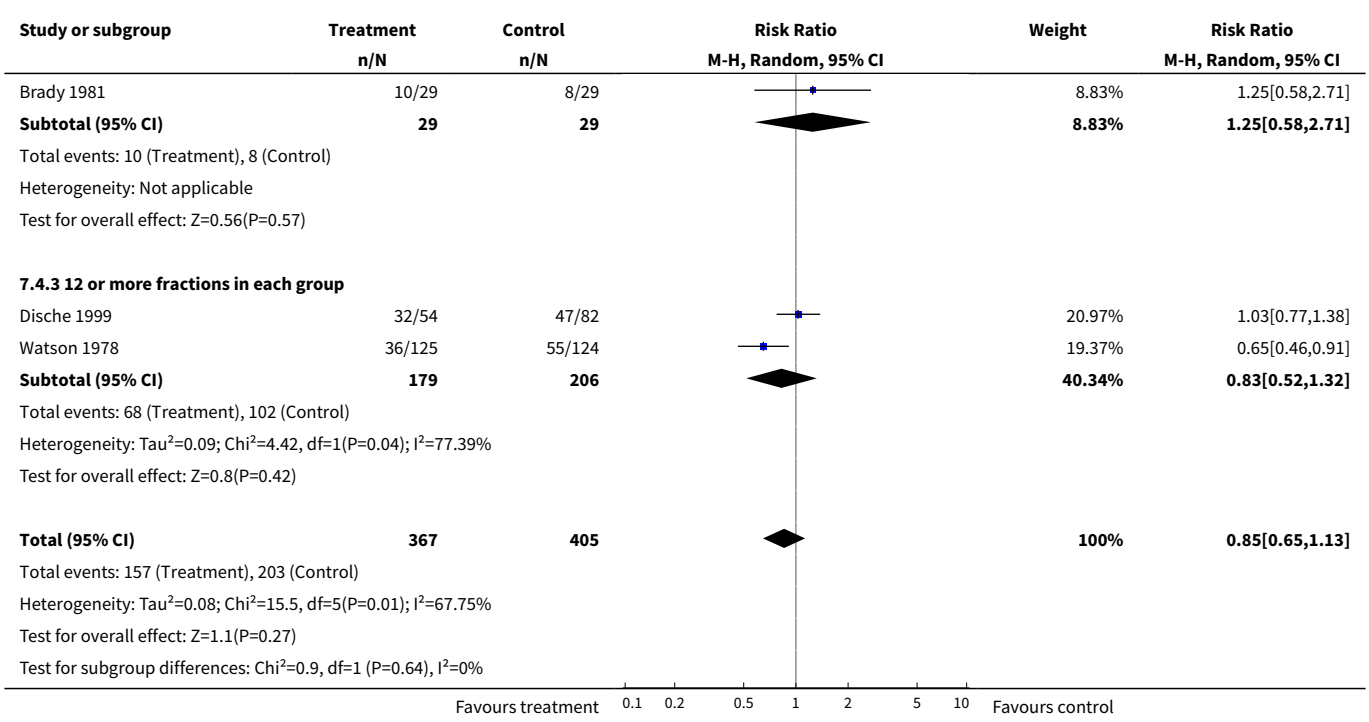


Analysis 7.3. Comparison 7 Local recurrence at five years, Outcome 3 Head and neck cancer - worst-case scenario.

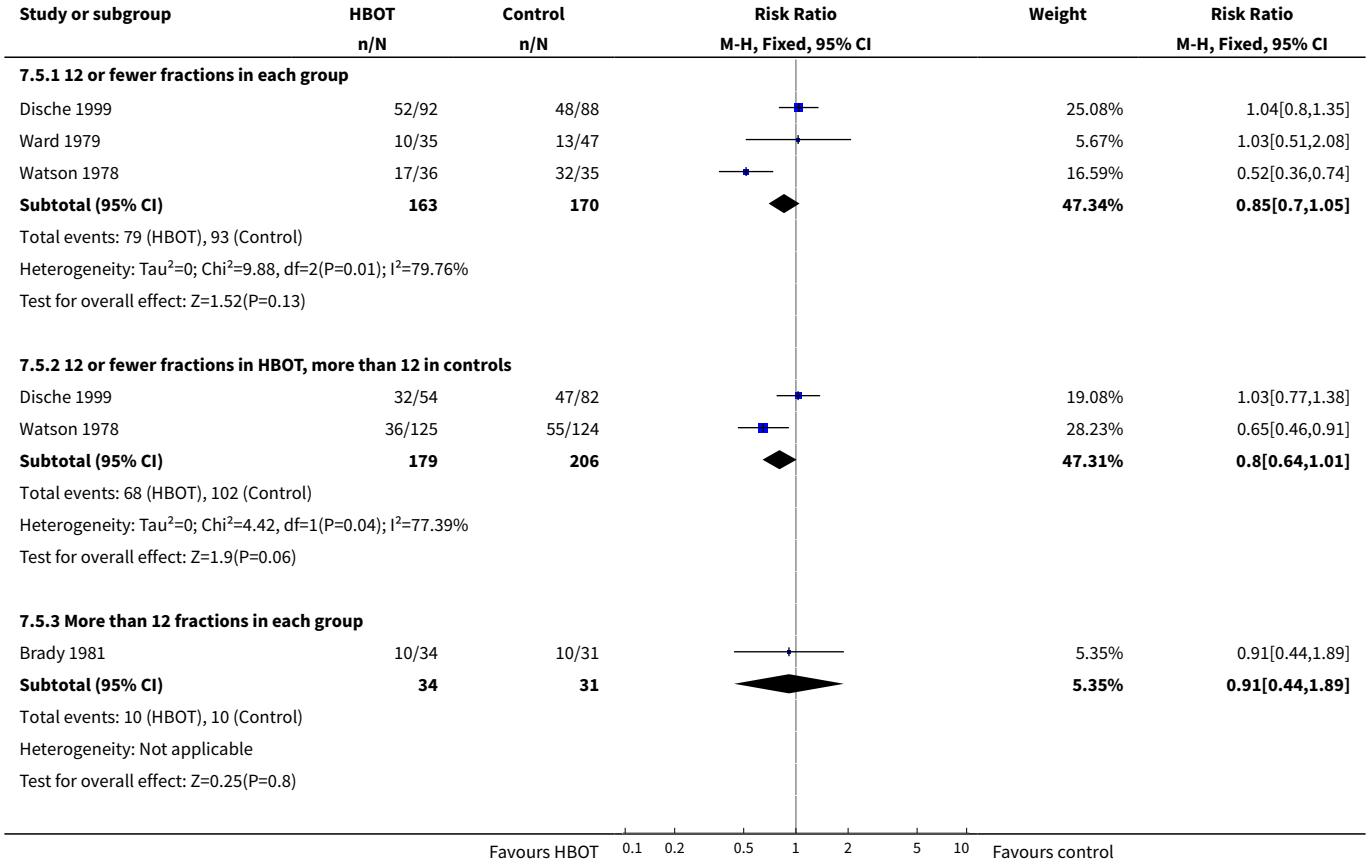


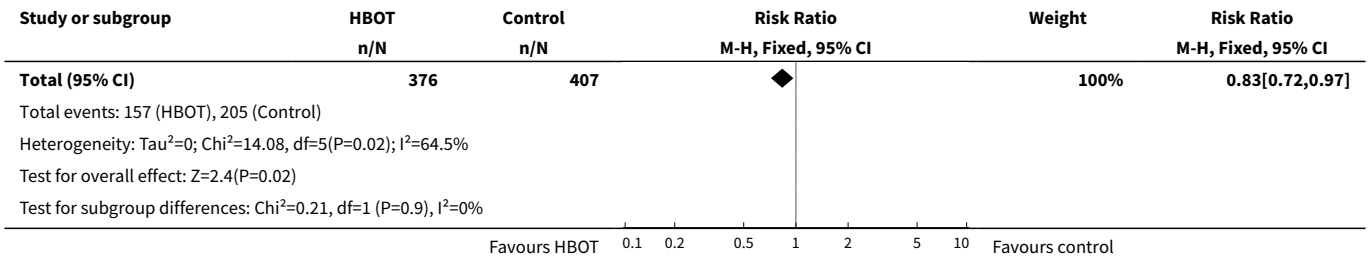
Analysis 7.4. Comparison 7 Local recurrence at five years, Outcome 4 Uterine cervix cancer.



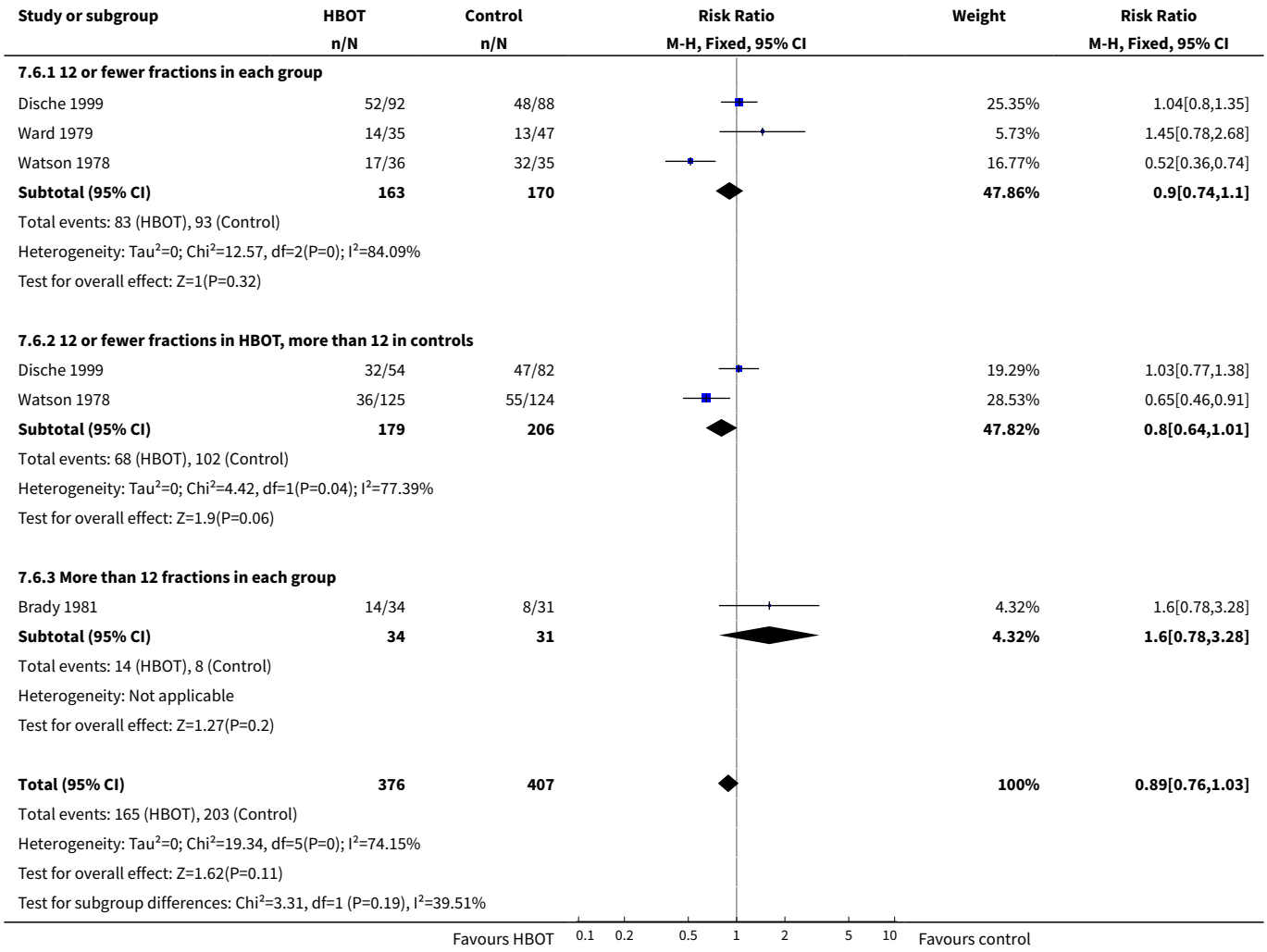


Analysis 7.5. Comparison 7 Local recurrence at five years, Outcome 5 Uterine cervix cancer - best-case scenario.





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

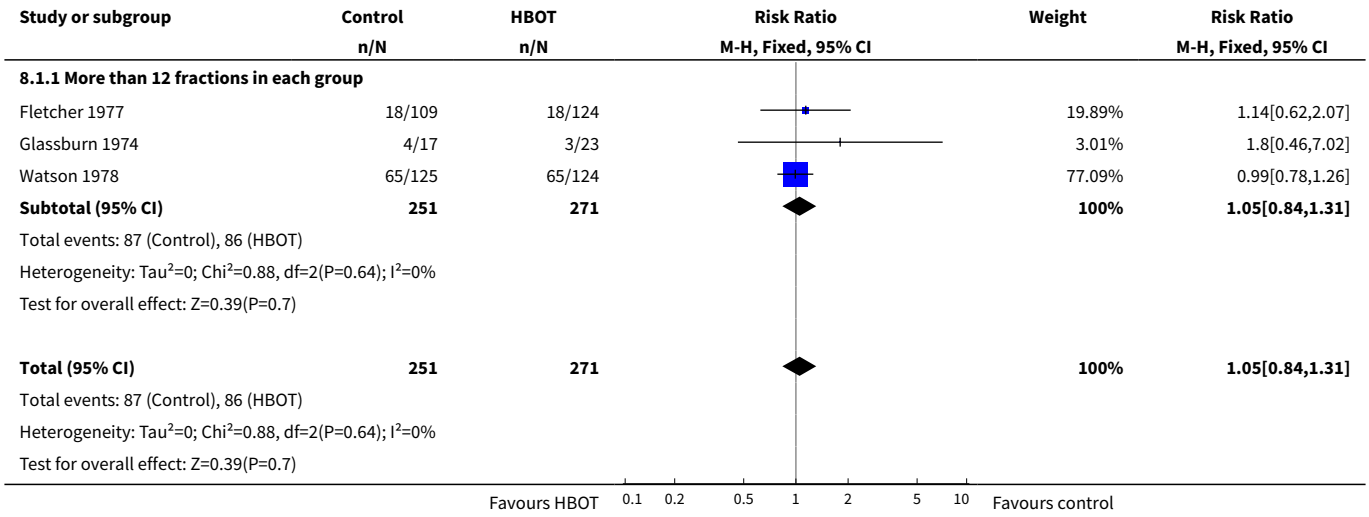


Comparison 8. Metastases at two years

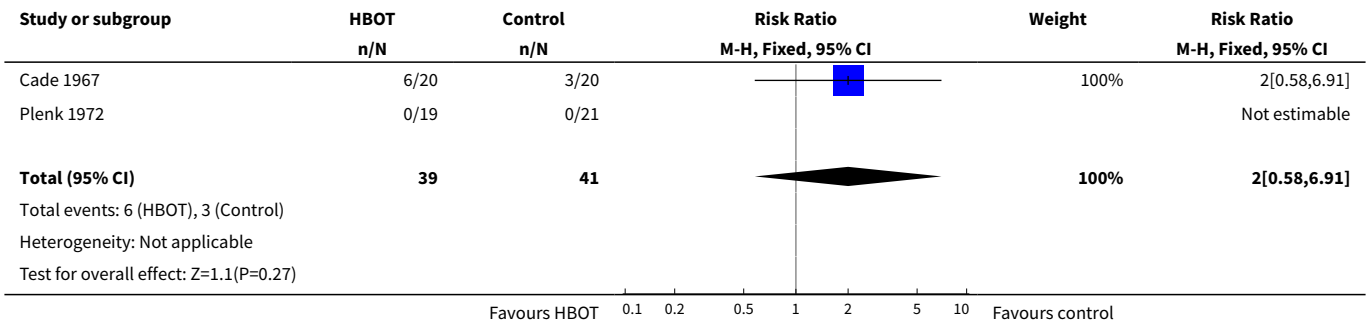
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Uterine cervix cancer	3	522	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.84, 1.31]

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

Analysis 8.1. Comparison 8 Metastases at two years, Outcome 1 Uterine cervix cancer.



Analysis 8.2. Comparison 8 Metastases at two years, Outcome 2 Urinary bladder carcinoma.

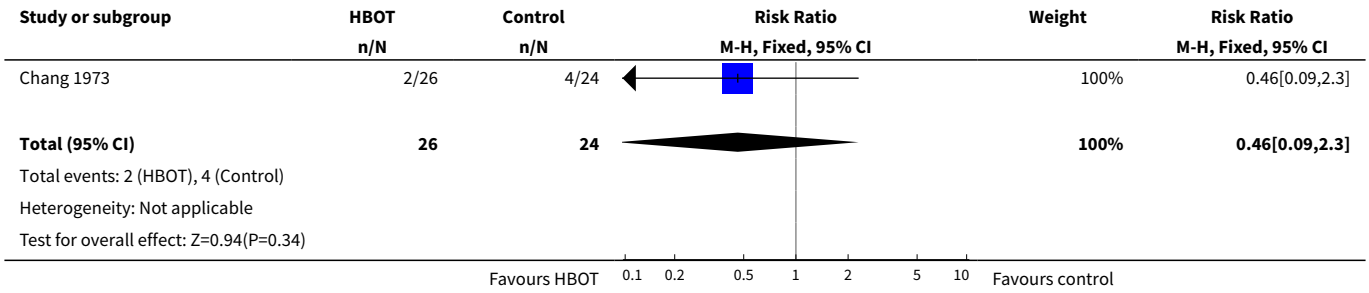


Comparison 9. Metastases at five years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Head and neck carcinoma	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.09, 2.30]

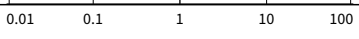
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Uterine cervix cancer	3	456	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.50, 1.26]
2.1 12 or fewer fractions each group	2	149	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.45, 0.99]
2.2 12 or fewer fractions in HBOT group versus more than 12 fractions in control	1	58	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.12]
2.3 More than 12 fractions in each group	1	249	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.78, 1.26]
3 Uterine cervix cancer - best-case scenario	3	467	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.46, 1.26]
3.1 12 or fewer fractions in each group	2	153	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.45, 0.98]
3.2 12 or fewer fractions in HBOT versus more than 12 in control	1	65	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.79]
3.3 More than 12 fractions in each group	1	249	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.78, 1.26]
4 Uterine cervix cancer - worst-case scenario	3	467	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.56, 1.31]
4.1 12 or fewer fractions in each group	2	153	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.35, 2.68]
4.2 12 or fewer fractions in HBOT versus more than 12 in control	1	65	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.11, 1.38]
4.3 More than 12 fractions in each group	1	249	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.78, 1.26]

Analysis 9.1. Comparison 9 Metastases at five years, Outcome 1 Head and neck carcinoma.



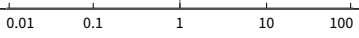
Analysis 9.2. Comparison 9 Metastases at five years, Outcome 2 Uterine cervix cancer.

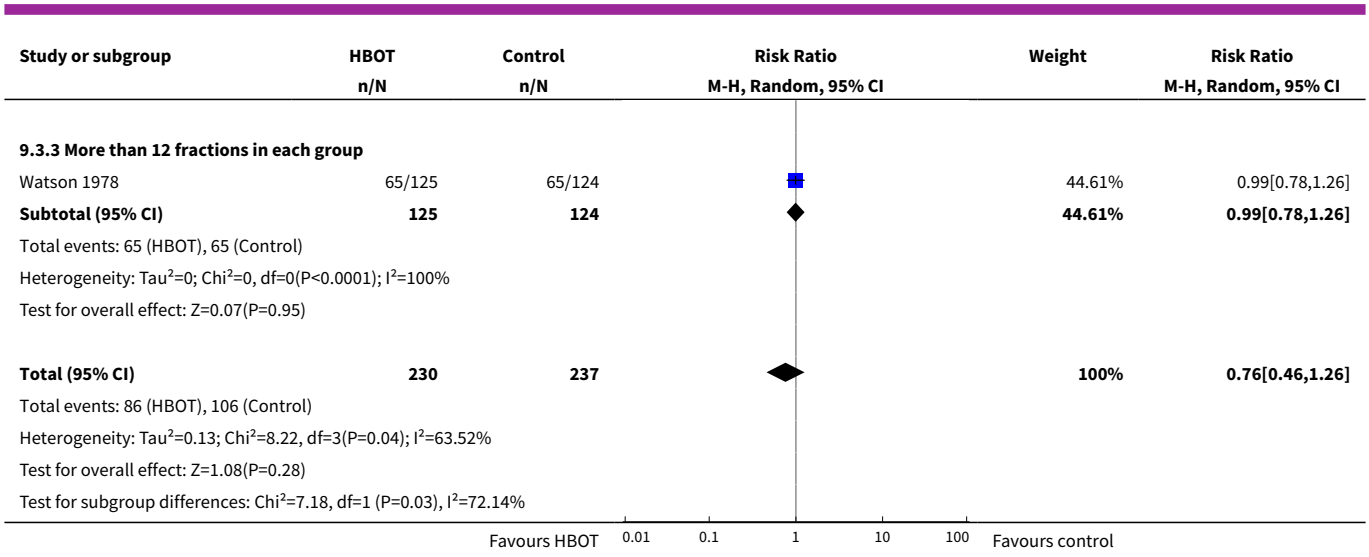
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.2.1 12 or fewer fractions each group					
Ward 1979	5/31	7/47		14.21%	1.08[0.38,3.11]
Watson 1978	16/36	25/35		36.83%	0.62[0.41,0.95]
Subtotal (95% CI)	**67**	**82**		**51.04%**	**0.67[0.45,0.99]**
Total events: 21 (HBOT), 32 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.98, df=1(P=0.32); I^2=0%					
Test for overall effect: Z=2(P=0.05)					
9.2.2 12 or fewer fractions in HBOT group versus more than 12 fractions in control					
Brady 1981	0/29	7/29		2.59%	0.07[0,1.12]
Subtotal (95% CI)	**29**	**29**		**2.59%**	**0.07[0,1.12]**
Total events: 0 (HBOT), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.88(P=0.06)					
9.2.3 More than 12 fractions in each group					
Watson 1978	65/125	65/124		46.37%	0.99[0.78,1.26]
Subtotal (95% CI)	**125**	**124**		**46.37%**	**0.99[0.78,1.26]**
Total events: 65 (HBOT), 65 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.07(P=0.95)					
Total (95% CI)	**221**	**235**		**100%**	**0.79[0.5,1.26]**
Total events: 86 (HBOT), 104 (Control)					
Heterogeneity: Tau^2=0.11; Chi^2=7.17, df=3(P=0.07); I^2=58.14%					
Test for overall effect: Z=1(P=0.32)					
Test for subgroup differences: Chi^2=6.03, df=1 (P=0.05), I^2=66.86%					



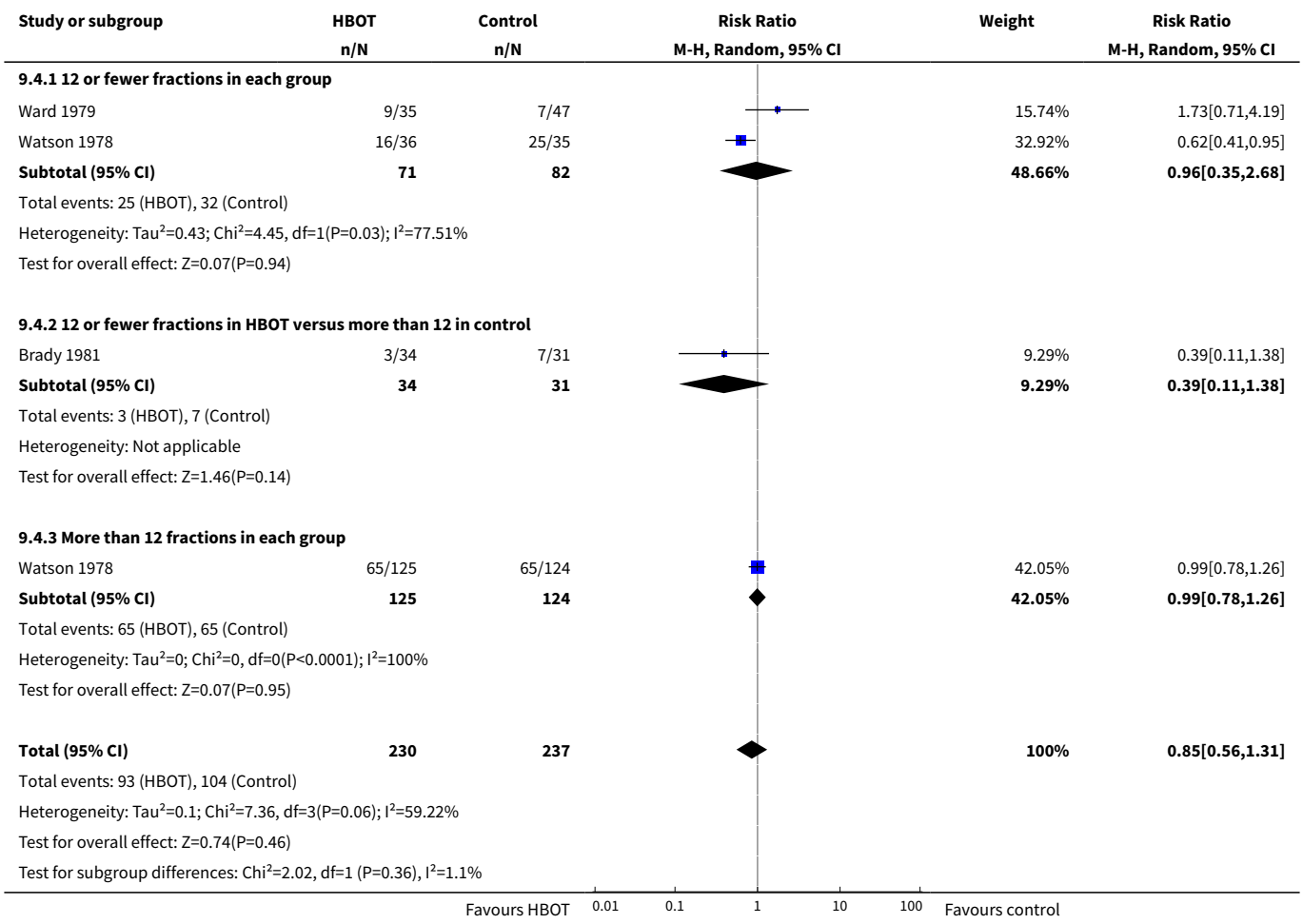
Analysis 9.3. Comparison 9 Metastases at five years, Outcome 3 Uterine cervix cancer - best-case scenario.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.3.1 12 or fewer fractions in each group					
Ward 1979	5/35	7/47		15.53%	0.96[0.33,2.77]
Watson 1978	16/36	25/35		36.82%	0.62[0.41,0.95]
Subtotal (95% CI)	**71**	**82**		**52.35%**	**0.66[0.45,0.98]**
Total events: 21 (HBOT), 32 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.59, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=2.08(P=0.04)					
9.3.2 12 or fewer fractions in HBOT versus more than 12 in control					
Brady 1981	0/34	9/31		3.04%	0.05[0,0.79]
Subtotal (95% CI)	**34**	**31**		**3.04%**	**0.05[0,0.79]**
Total events: 0 (HBOT), 9 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.12(P=0.03)					





Analysis 9.4. Comparison 9 Metastases at five years, Outcome 4 Uterine cervix cancer - worst-case scenario.



Comparison 10. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death through radiation tissue injury	2	633	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.89, 3.03]
2 Severe radiation tissue injury	7	779	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.66, 3.33]
2.1 Cancers of the uterine cervix	3	456	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [1.22, 3.46]
2.2 Cancers of head and neck	4	323	Risk Ratio (M-H, Fixed, 95% CI)	2.64 [1.65, 4.23]
3 Severe radiation tissue injury - best-case scenario	7	803	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.39, 2.69]
4 Severe radiation tissue injury - worst-case scenario	7	803	Risk Ratio (M-H, Fixed, 95% CI)	2.69 [1.92, 3.77]
5 Acute central nervous system oxygen toxicity	4	331	Risk Ratio (M-H, Fixed, 95% CI)	6.76 [1.16, 39.31]
5.1 Mixed cancers (bronchus, bladder, cervix)	2	129	Risk Ratio (M-H, Fixed, 95% CI)	10.76 [0.61, 188.98]
5.2 Cancers of the head and neck	2	202	Risk Ratio (M-H, Fixed, 95% CI)	4.30 [0.47, 39.60]
6 Acute central nervous system toxicity - best-case scenario	4	337	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.81, 11.10]
6.1 12 or fewer oxygen fractions	3	248	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.26, 6.53]
6.2 More than 12 oxygen fractions	1	89	Risk Ratio (M-H, Fixed, 95% CI)	10.76 [0.61, 188.98]
7 Acute central nervous system toxicity - worst-case scenario	4	337	Risk Ratio (M-H, Fixed, 95% CI)	9.74 [1.73, 54.98]
7.1 12 or fewer oxygen fractions	3	248	Risk Ratio (M-H, Fixed, 95% CI)	9.12 [1.05, 79.50]
7.2 More than 12 oxygen fractions	1	89	Risk Ratio (M-H, Fixed, 95% CI)	10.76 [0.61, 188.98]
8 Middle ear barotrauma	1	89	Risk Ratio (M-H, Fixed, 95% CI)	6.85 [0.36, 128.83]

Analysis 10.1. Comparison 10 Adverse events, Outcome 1 Death through radiation tissue injury.

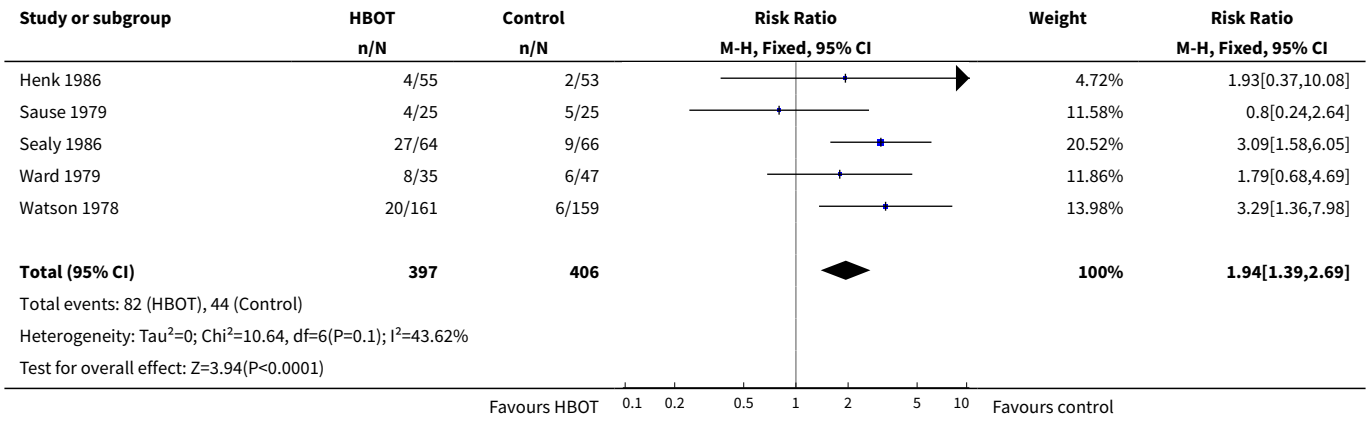
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dische 1999	15/146	12/167		73.55%	1.43[0.69,2.95]
Watson 1978	9/161	4/159		26.45%	2.22[0.7,7.07]
Total (95% CI)	**307**	**326**		**100%**	**1.64[0.89,3.03]**
Total events: 24 (HBOT), 16 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.4, df=1(P=0.53); I^2=0%					
Test for overall effect: Z=1.58(P=0.11)					

Analysis 10.2. Comparison 10 Adverse events, Outcome 2 Severe radiation tissue injury.

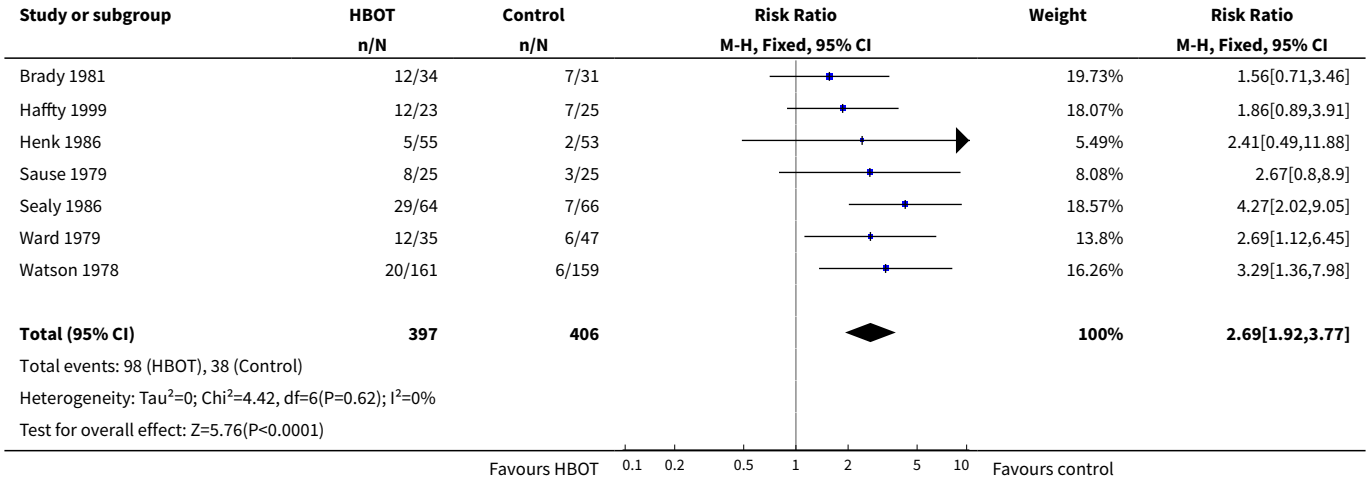
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
10.2.1 Cancers of the uterine cervix					
Brady 1981	7/29	7/29		19.35%	1[0.4,2.49]
Ward 1979	8/31	6/47		13.19%	2.02[0.78,5.26]
Watson 1978	20/161	6/159		16.69%	3.29[1.36,7.98]
Subtotal (95% CI)	**221**	**235**		**49.23%**	**2.05[1.22,3.46]**
Total events: 35 (HBOT), 19 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.48, df=2(P=0.18); I^2=42.49%					
Test for overall effect: Z=2.7(P=0.01)					
10.2.2 Cancers of head and neck					
Haffty 1999	12/23	7/25		18.55%	1.86[0.89,3.91]
Henk 1986	4/54	2/53		5.58%	1.96[0.38,10.27]
Sause 1979	4/21	3/23		7.92%	1.46[0.37,5.78]
Sealy 1986	27/60	7/64		18.73%	4.11[1.94,8.74]
Subtotal (95% CI)	**158**	**165**		**50.77%**	**2.64[1.65,4.23]**
Total events: 47 (HBOT), 19 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.02, df=3(P=0.39); I^2=0.7%					
Test for overall effect: Z=4.04(P<0.0001)					
Total (95% CI)	**379**	**400**		**100%**	**2.35[1.66,3.33]**
Total events: 82 (HBOT), 38 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.03, df=6(P=0.32); I^2=14.63%					
Test for overall effect: Z=4.8(P<0.0001)					
Test for subgroup differences: Chi^2=0.5, df=1 (P=0.48), I^2=0%					

Analysis 10.3. Comparison 10 Adverse events, Outcome 3 Severe radiation tissue injury - best-case scenario.

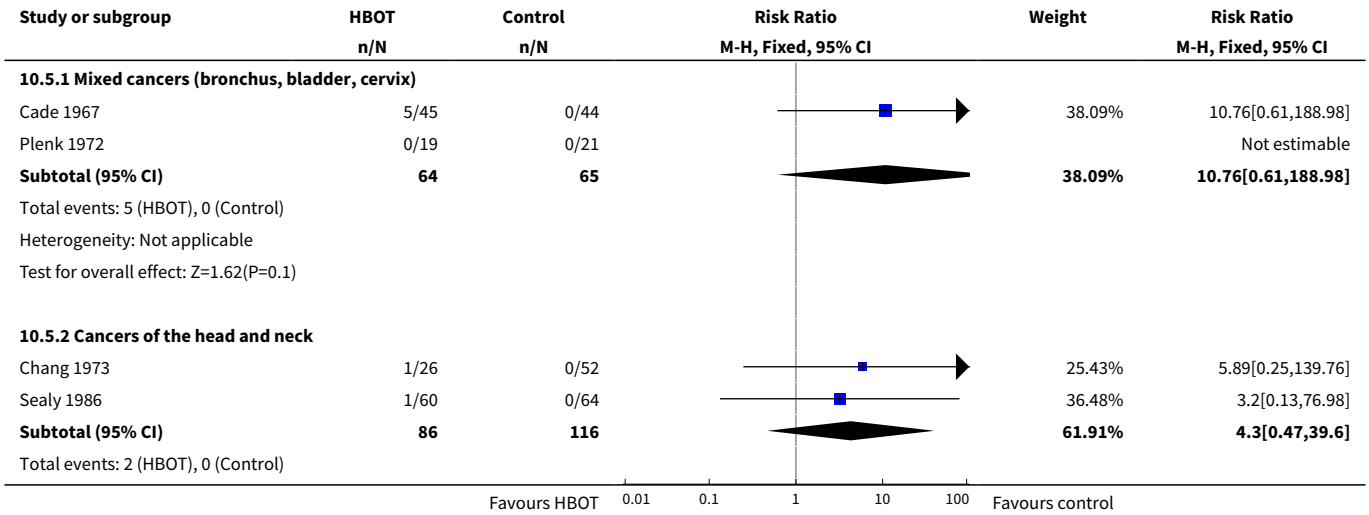
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Brady 1981	7/34	9/31		21.8%	0.71[0.3,1.67]
Haffty 1999	12/23	7/25		15.54%	1.86[0.89,3.91]

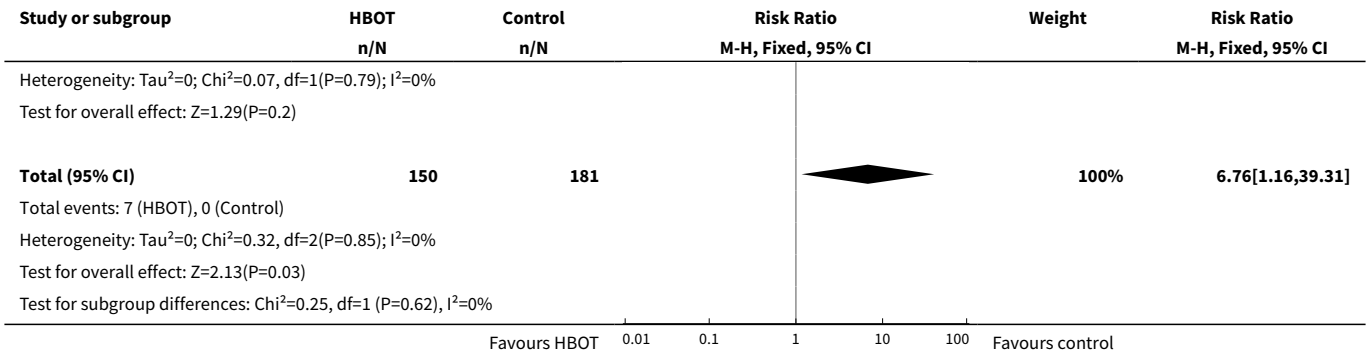


Analysis 10.4. Comparison 10 Adverse events, Outcome 4 Severe radiation tissue injury - worst-case scenario.

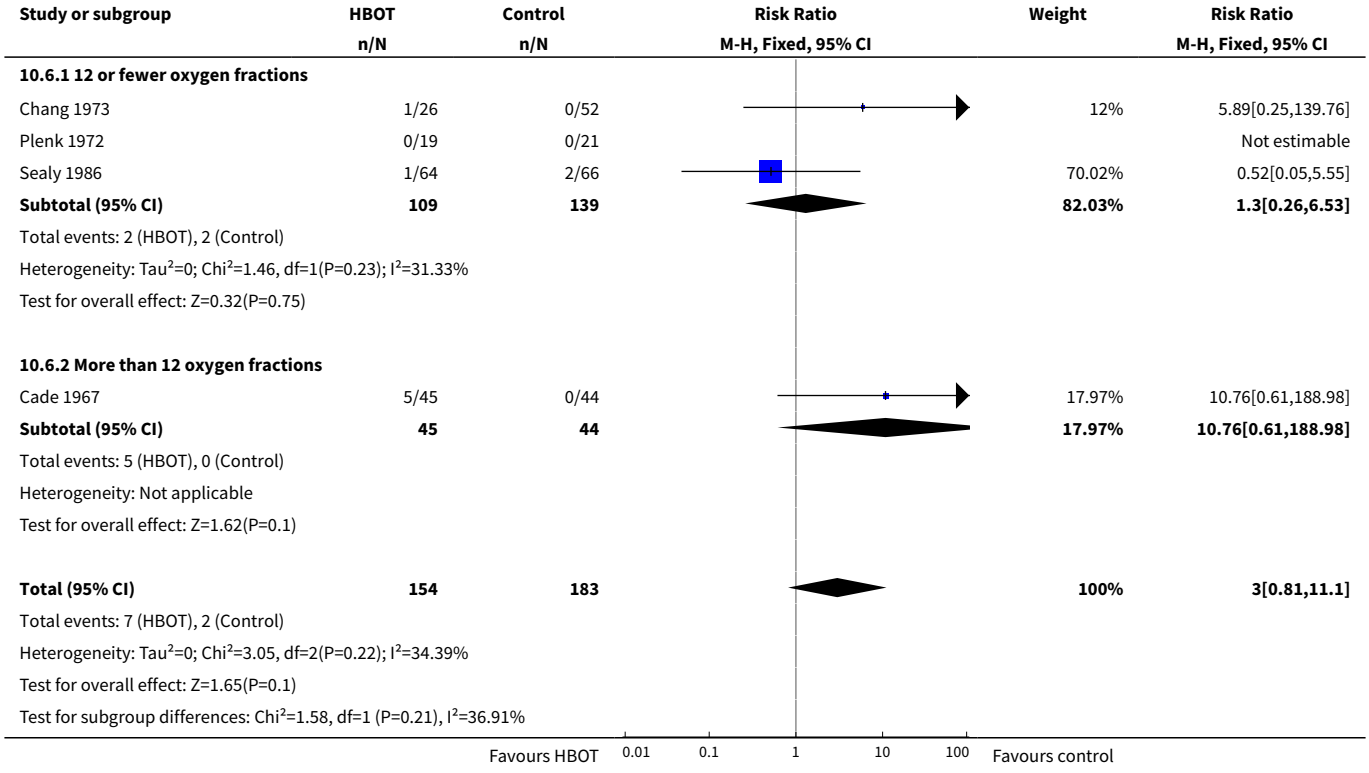


Analysis 10.5. Comparison 10 Adverse events, Outcome 5 Acute central nervous system oxygen toxicity.

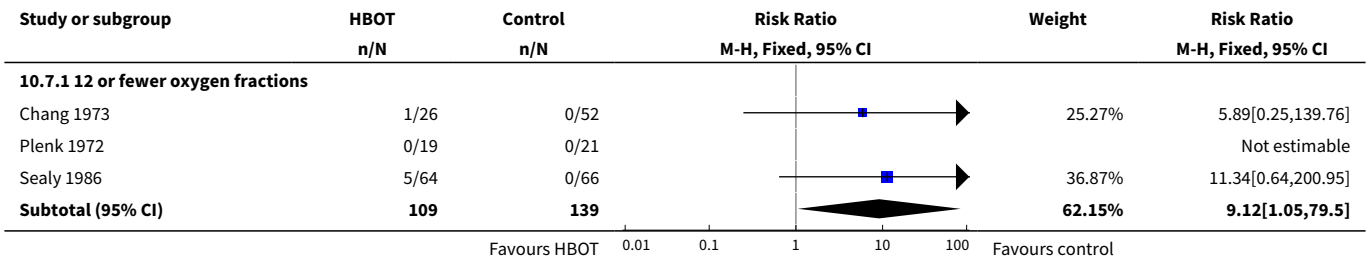


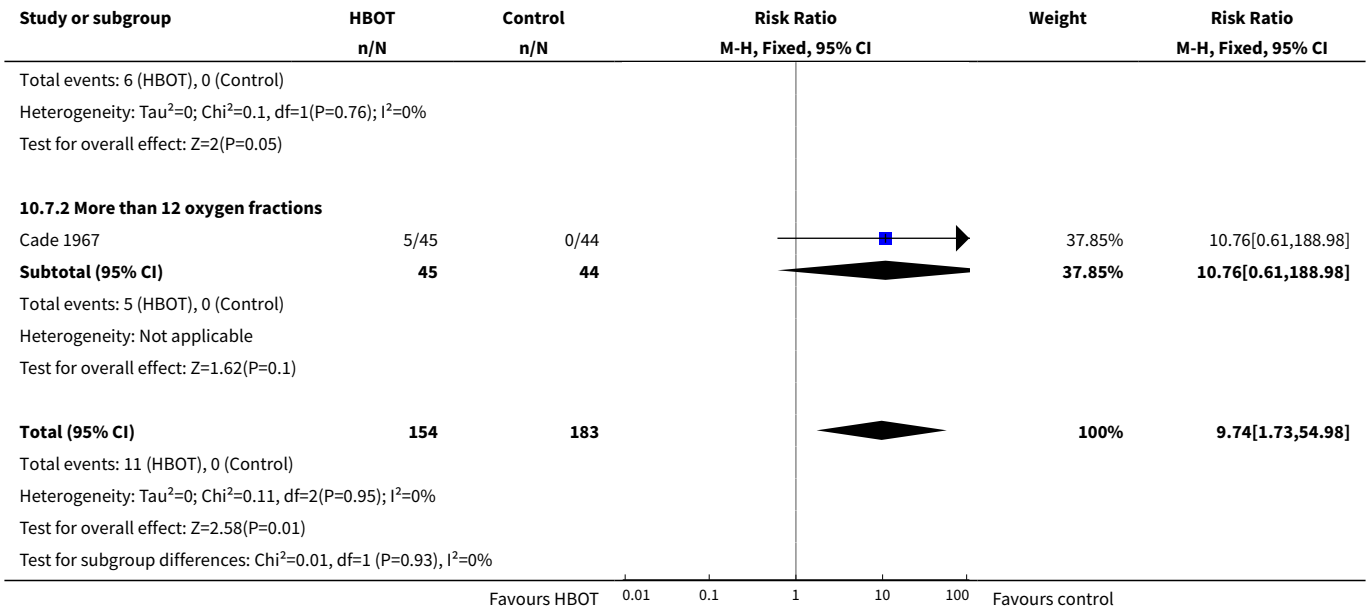


Analysis 10.6. Comparison 10 Adverse events, Outcome 6 Acute central nervous system toxicity - best-case scenario.

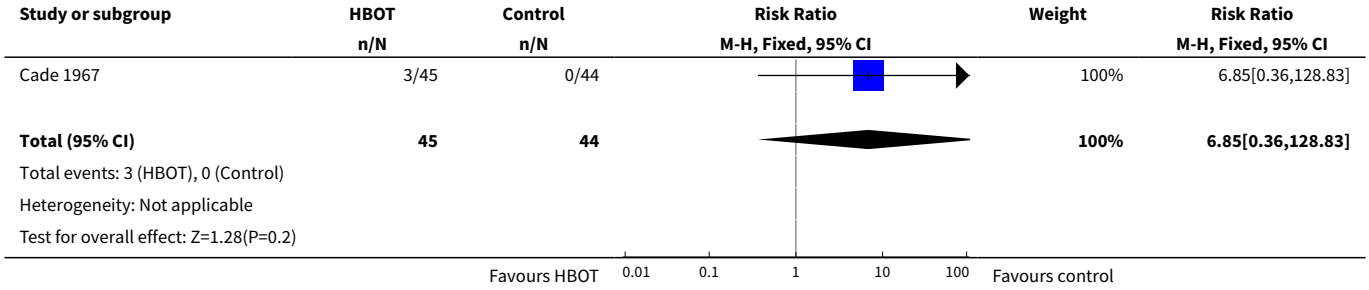


Analysis 10.7. Comparison 10 Adverse events, Outcome 7 Acute central nervous system toxicity - worst-case scenario.





Analysis 10.8. Comparison 10 Adverse events, Outcome 8 Middle ear barotrauma.



APPENDICES

Appendix 1. MEDLINE search strategy

1 Hyperbaric Oxygenation/
2 (hyperbaric and oxygen*).mp.
3 (hbo or hbot).mp.
4 (high adj3 (pressure or tension)).mp.
5 ((multiplace or monoplace) and chamber*).mp.
6 1 or 2 or 3 or 4 or 5
7 exp Radiotherapy/
8 radiotherap*.mp.
9 radiation.mp.
10 irradiat*.mp.
11 radiotherapy.fs.
12 7 or 8 or 9 or 10 or 11
13 randomized controlled trial.pt.
14 controlled clinical trial.pt.
15 randomized.ab.
16 placebo.ab.

17 clinical trials as topic.sh.
18 randomly.ab.
19 trial.ti.
20 13 or 14 or 15 or 16 or 17 or 18 or 19
21 6 and 12 and 20

key:

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

Appendix 2. Embase search strategy

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

key:
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer

Appendix 3. CINAHL search strategy

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

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

Appendix 4. CENTRAL search strategy

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

WHAT'S NEW

Date	Event	Description
17 July 2018	Amended	Next stage expected date amended.
28 June 2018	Review declared as stable	No new studies anticipated in this area.

HISTORY

Protocol first published: Issue 1, 2004
Review first published: Issue 4, 2005

Date	Event	Description
27 March 2018	New citation required but conclusions have not changed	Update of search, methodology, and reporting of results. We have updated references in the Background, completed the 'Risk of bias' tables, modified the Plain language summary, and added 'Summary of findings' tables. Abstract, 'Summary of findings' tables and summary of main results are concordant. No new studies identified.
5 September 2017	New search has been performed	Search updated 5 September 2017.
21 February 2012	New citation required but conclusions have not changed	New searches executed in March 2011, but no new studies identified.
6 January 2012	New search has been performed	Text updated and study flow diagram added.
4 October 2008	New search has been performed	Review updated, no new trials identified when searches were re-run on 27 September 2008.

Date	Event	Description
16 July 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Michael Bennett: principal author, conception, search strategy and execution, data extraction and critical appraisal, hyperbaric medicine content expert, statistical analysis.
John Feldmeier: co-author, radiation oncology and hyperbaric medicine content expert.
Robert Smee: co-author, data extraction and critical appraisal, radiation oncology content expert.
Chris Milross: co-author Background and Discussion, radiation oncology content expert.

DECLARATIONS OF INTEREST

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

SOURCES OF SUPPORT

Internal sources

- No specific support provided, Australia.

External sources

- No sources of support, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans; Male