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## [Intervention Review]

## Hyperbaric oxygenation for tumour sensitisation to radiotherapy

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## **ABSTRACT**

## **Background**

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

## **Objectives**

To assess the benefits and harms of 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.