NHS England

Evidence review: Hyperbaric Oxygen Therapy for Soft Tissue Radiation Damage in Patients with a History of Pelvic Irradiation for Malignant Disease

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Contents

1 Introduction

Introduction

- Radiation therapy can damage normal tissue in the radiated area. This normally heals spontaneously following completion of the radiotherapy treatment however serious radiation-related complications can develop months or years later (Bennett et al 2016). This can result in fibrosis, ulceration or areas of cell death (radiation necrosis). Late tissue radiation damage can significantly reduce quality of life and can be life threatening (Bennett et al 2016).
- Areas that are particularly sensitive to soft tissue radiation damage are the pelvis, especially the rectum, and the skin and mucosa of the head and neck (Hoggan & Cameron 2014).
- Pelvic radiation disease is defined as “transient or long-term problems ranging from mild to severe, arising in non-cancerous tissues resulting from radiotherapy treatment to a tumour of pelvic origin” (van de Wetering et al 2016).
- Radiation proctopathy is the most commonly investigated late-radiation effect to the pelvis with common symptoms including rectal urgency, rectal incontinence, pain, strictures, mucus discharge and rectal bleeding (van de Wetering et al 2016). Symptoms associate with pelvic radiation can also include bloating, flatulence and diarrhoea (Glover et al 2016). The pathophysiology and symptomatology of radiation proctopathy are complex because different anorectal sub-regions can be involved (van de Wetering et al 2016).
- Haemorrhagic cystitis is “a diffuse inflammatory condition of the bladder due to an infectious or non-infectious aetiology resulting in bleeding from the bladder mucosa” and is a “relatively common and potentially severe complication of high-dose chemoradiotherapy for the treatment of pelvic malignancies” (Shao et al 2011). The clinical manifestation of this condition can vary from microscopic haematuria to severe haemorrhage with clot formation and urinary tract obstruction. This can lead to “hydronephrosis and acute renal failure when it becomes chronic and recurrent” (Shao et al 2011). Symptoms can include urinary frequency, urgency and pelvic pain (Shao et al 2011).

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- NICE have not published any guidance on the treatment of soft tissue radiation damage or the use of hyperbaric oxygen therapy.

The indication and epidemiology

- Late radiation tissue injury affects between 5% and 15% of long time survivors who received radiotherapy with the incidence varying with dose, age and treatment site (Bennett et al 2016). In patients who have received radiotherapy for pelvic cancer, up to a third subsequently develop chronic moderate or severe gastrointestinal symptoms (Glover et al 2016)..Between 4% and 22% of patients receiving pelvic radiotherapy will develop significant soft tissue radiation injury affecting quality of life, however the true incidence is likely to be higher due to insufficient long-term follow-up, frequent lack of recognition and social stigma (NHS England 2017). No data were identified for the proportion of patients that have symptoms that are not relieved or rendered manageable by standard interventions.

Standard treatment and pathway of care

- Treatments for late tissue radiation damage include symptom management and surgery to remove or repair the affected area (Bennett et al 2016). Surgical intervention in an area that has received radiation therapy is associated with an increased incidence of delayed healing, infection or breakdown of the surgical wound (Bennett et al 2016).
- Non-surgical options include aminosalicylic acid derivatives (such as sulfasalazine and mesalazine), short chain fatty acid preparations, sucralfate preparations, coagulation therapy, corticosteroids,

formalin applications, pentoxyfilline, antibiotic treatment, hyperbaric oxygen therapy, retinol palmitate and Chinese traditional medicine in combination with Western medicine (van de Wetering et al 2016).

- Management strategies for patients whose condition fails to respond to standard interventions remain unclear and lacking in good quality evidence (NHS England 2017).

The intervention (and licensed indication)

- In hyperbaric oxygen therapy (HBOT) patients receive 100% oxygen inside a pressurised treatment chamber (Hoggan & Cameron 2014). Treatments typically involve pressurisation of between 2.0 and 2.5 atmosphere absolute (ATA) (203 to 253 kilopascal (kPa)[1]) for between 60 and 120 minutes once or twice daily for a total of 30 to 60 sessions (Bennett et al 2016).

Rationale for use

- The aim of HBOT is to increase the number of blood vessels in irradiated tissue, improve tissue quality, promote healing and prevent breakdown of irradiated areas (Bennett et al 2016).

2 Summary of results

- This evidence review found two randomised controlled trials comparing HBOT to sham treatment, one randomised controlled trial comparing HBOT to intravesical hyaluronic acid instillation (HA) and one non-randomised controlled study comparing HBOT to argon plasma coagulation (APC).
- The studies considered different outcomes and reported outcomes at different time periods following treatment. Outcomes most commonly related to changes in the symptoms experienced by patients.
- The most recent trial with 84 patients considered outcomes of gastrointestinal symptoms, rectal bleeding and bowel dysfunction. This study did not find any significant differences in the outcomes for patients receiving HBOT and patients receiving sham treatment 12 months after the treatment (Glover et al 2016).
- The largest trial with 150 patients found a greater improvement in LENT SOMA score (a scoring system for severity of radiation-induced complications) for the HBOT group than the sham group immediately following treatment (an improvement of 5.00 points for HBOT and 2.61 points for sham) (Clarke et al 2008).

[1] 1 ATA = 101.3 kPa

- This study also found that a greater proportion of HBOT patients showed at least some improvement on clinical evaluation immediately following treatment (89% vs 63%) (Clarke et al 2008). Four categories were used for clinical improvement: healed, significant improvement, moderate improvement or no improvement. The proportion of patients that were considered healed in each group was 8% for HBOT and 0% for sham. No definition was provided to explain what was meant by a moderate or significant improvement.
- Quality of life outcomes were reported in one trial (Clarke et al 2008). This found no difference between HBOT and sham patients in general well-being assessed immediately after treatment. The study did find that the HBOT group had a greater improvement from baseline (14%) than the sham group (5%) on a bowel bother scale. However the HBOT group had a lower score at baseline and the bowel bother scores were similar for both groups immediately following treatment (approximately 60%).
- The evidence review also found two small studies that compared HBOT to other treatments. These were intravesical hyaluronic acid instillation (HA) in patients with haemorrhagic cystitis (Shao et al 2011) and argon plasma coagulation (APC) in patients with radiation proctopathy (Álvaro-Villegas et al 2011).
- Shao et al (2011) found no significant difference between HBOT and HA in the proportion of patients showing a partial or complete response to treatment (75% in both groups at final follow-up 18 months after treatment).
- No direct comparison of the two groups was done for the other outcomes reported by Shao et al (2011) of voiding (urinating) frequency and pelvic pain. An improvement from baseline was seen in both groups for voiding frequency at six months (by approximately one to three voids per day from a baseline of approximately 10 voids per day). However this improvement was not sustained over the 18 month follow-up period. An improvement in pelvic pain from baseline was seen in both groups at six, 12 and 18 months. This improvement was approximately one point on a 10-point pain scale from a baseline of approximately two to three points.
- Álvaro-Villegas et al (2011) found no significant difference between HBOT and APC for change in haemoglobin level at one, two or three months follow-up. For the other two outcomes assessed (number of transfusions and tissue toxicity) the improvement was greater in the APC group in the first two months. By three months the HBOT group had also improved and there was no significant difference between the groups. In both groups the number of transfusions required ranged from approximately four to five at baseline to less than one at three months follow-up. The time period over which transfusions were received was not specified.
- One study reported a significantly higher incidence of urinary tract infection (UTI) in the HA group (43%) compared to the HBOT group (10%) at six months follow-up (Shao et al 2011). There was no significant difference between the groups at later follow-up with a UTI incidence of 50% for the HA group and 30% for the HBOT group at 18 months follow-up.
- Other studies did not report any analysis comparing the number of adverse events between HBOT and sham or other treatments.
- Common adverse events in patients receiving HBOT were eye changes including myopia (30% in one study) and ear pain (28% in one study).
- No studies assessing the cost effectiveness of HBOT for soft tissue radiation damage were identified.

- There were limitations in the studies reported. The two trials comparing HBOT to sham did not include all patients in their analysis, reducing confidence in their results, and the study authors did not always include enough information to enable the reader to understand the importance of their results.
- Direct comparison between the studies is not possible due to the different comparators used, the different outcome measures reported and the different time periods used for the assessment of outcomes following treatment.
- At present there is inconsistent evidence about the efficacy of HBOT compared to sham in the treatment of soft tissue radiation damage following pelvic irradiation. Further adequately powered trials comparing HBOT to sham may be warranted.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: PubMed, Embase, Cochrane Library, TRIP and NHS Evidence (see section 10 for search strategy).
- The search dates for publications were between 1st January 2007 and 24th April 2017.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Systematic reviews on HBOT for soft tissue radiation damage were identified by the literature search (Bennett et al 2016; Hoggan & Cameron 2014). When systematic reviews are available they would normally be used as the primary source of evidence for a review. However, the two systematic reviews identified were not specific to patients who had received pelvic irradiation, used different comparators and did not include any pooled or meta-analysis relating to radiation tissue damage from pelvic irradiation. In addition, not all of the pelvic irradiation studies included in the systematic reviews met the criteria for the population specified in the PICO for this review. Therefore the evidence presented in this review is taken from individual studies meeting the PICO rather than from the systematic reviews.
- Evidence from randomised controlled trials and non-randomised controlled studies was available. Therefore uncontrolled observational studies, such as cohort studies and case series, were not included in this review.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using the National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8).

4 Results

A total of four papers matching the PICO were identified: one randomised double-blind sham-controlled trial (Glover et al 2016), one randomised double-blind sham-controlled crossover trial (Clarke et al 2008), one randomised controlled trial comparing HBOT to intravesical hyaluronic acid instillation (HA) (Shao et al 2011) and one non-randomised controlled study comparing HBOT to argon plasma coagulation (APC) (Álvaro-Villegas et al 2011). Two review papers were used for additional background information (Bennett et al 2016; Hoggan & Cameron 2014).

The studies ranged in size from 31 to 150 participants, with patients receiving at least 30 HBOT treatments at between 2.0 and 2.5 ATA (203 to 253 kPa) for 60 to 90 minutes. Full details of the study designs and outcomes are summarised in the evidence tables in section 7.

Clinical effectiveness

1. In the population of interest, what is the effect of adding HBOT into the standard management plan on the specified outcomes?

The outcome measures used varied between the studies. The outcomes reported in the studies comparing HBOT to sham included gastrointestinal symptoms, rectal bleeding, LENT SOMA score, clinical evaluation, bowel dysfunction and quality of life. The outcomes reported in the study comparing HBOT to HA included improvement in symptoms, voiding frequency and pelvic pain. The outcomes reported in the study comparing HBOT to APC included haemoglobin level, number of transfusions and tissue toxicity. Further details of the outcome measures used are provided in the tables in sections 7 and 8.

Gastrointestinal symptoms
One study reported change in gastrointestinal symptoms (Glover et al 2016). This found no significant difference between HBOT and sham at 12 months follow-up (p=0.50).

Rectal bleeding
One study reported change in rectal bleeding (Glover et al 2016). This found no significant difference between HBOT and sham at 12 months follow-up (p=0.09).

LENT SOMA score
One study reported change in mean LENT SOMA score (Clarke et al 2008). This found a significant improvement in mean LENT SOMA score from baseline to immediately following treatment for both the HBOT and sham groups (p<0.0001) with a greater improvement for the HBOT group (p=0.0019). The improvement in the HBOT group was 5.00 points and in the sham group the improvement was 2.61 points from baseline scores of 12.55 and 12.84 respectively. In a direct comparison between the groups, HBOT had significantly better average scores (p=0.0150) with an estimated difference between the groups of 1.93 (95%CI 0.38 to 3.48). The mean scores of the sham group improved after they had crossed over to HBOT treatment.

Clinical evaluation
One study reported the proportion of patients showing at least some improvement on clinical evaluation immediately following treatment (Clarke et al 2008). This found that a significantly greater proportion of HBOT patients (89%) showed at least some improvement on clinical evaluation compared to sham patients (63%) (p=0.0009) (OR 5.93 95%CI 2.04 to 17.24). The proportion of patients that were considered healed in each group was 8% for HBOT and 0% for sham. No definition was provided for the other categories of improvement (moderate or significant).

Bowel dysfunction
One study reported change in bowel dysfunction (Glover et al 2016). This found no significant difference between HBOT and sham for rectal (p=0.12) or intestinal (p=0.20) adverse effects at 12 months follow-up.

Quality of life
One study reported analysis of quality of life outcomes immediately following treatment (Clarke et al 2008). This found no difference between HBOT and sham in general well-being (p value not reported). A significant improvement from baseline on a bowel bother scale was reported for the HBOT group (14%) (p=0.0007) but not for the sham group (5%) (p=0.1521). However the HBOT group had a lower score at baseline so the bowel bother scores were similar for both groups immediately following treatment (approximately 60%). Change in bowel function score was described but no statistical analysis was reported. No statistical analyses comparing HBOT to sham was reported for quality of life outcomes.

Improvement in symptoms
One study reported the proportion of patients showing a partial or complete response to treatment (Shao et al 2011). The definitions used for a partial or complete response are provided in the tables in sections 7 and 8. This found no significant difference between HBOT and HA instillation at six, 12 or 18 months follow-up (p>0.05), with 75% of both groups showing a partial or complete response at final follow-up 18 months after treatment.

Voiding frequency
One study reported change in bladder voiding frequency (number per day) (Shao et al 2011). This found a statistically significant improvement from baseline in both the HBOT and HA instillation groups at six months follow-up (p<0.01). For the HBOT group the number of voids per day decreased by a mean ± standard deviation of 1.2 ± 1.1 from a baseline of 9.8 ± 1.7. For the HA group the number of voids per day decreased by 2.9 ± 1.7 from a baseline of 10.4 ± 1.8. This improvement was reduced but still statistically significant at 12 months for the HA group (p<0.01) but not for the HBOT group. By 12 months the mean improvement in voids per day had decreased to 0.2 for the HBOT group. For the HA group the mean improvement in voids per day had decreased to 0.2 by 18 months follow-up. No direct comparison between HBOT and HA instillation was reported for voiding frequency.

Pelvic pain
One study reported change in pelvic pain using a scale of one to 10 (Shao et al 2011). This found a statistically significant improvement from baseline for both HBOT and HA instillation at six months, 12 months and 18 months (p<0.05). For the HBOT group the mean ± standard deviation improvement at six months was 0.9 ± 0.8 from a baseline of 2.5 ± 2.2. The mean improved further at 18 months to 1.2 ± 1.2. For the HA group the greatest improvement was seen at 18 months with an improvement of 1.5 ± 1.2 from a baseline of 2.8 ± 2.2. No direct comparison between HBOT and HA instillation was reported for change in pelvic pain.

Haemoglobin level
One study reported change in haemoglobin level (Álvaro-Villegas et al 2011). This found no significant difference between HBOT and APC at one, two or three months follow-up (p>0.05).

Number of transfusions
One study reported change in number of transfusions (Álvaro-Villegas et al 2011). This showed that APC had a statistically significantly greater reduction in mean number of transfusions required compared to HBOT at one and two months follow-up (p<0.05). At three months follow-up the number of transfusions required had reduced in both groups from a baselines of 4.8 ± 7.8

(APC) and 3.8 ± 2.9 (HBOT) to 0.6 ± 0.9 (APC) and 0.8 ± 1.2 (HBOT). The difference between the groups was no longer statistically significant at three months ($p>0.05$).

Tissue toxicity

One study reported change in tissue toxicity (Álvaro-Villegas et al 2011). This showed that APC had a statistically significantly greater reduction in mean tissue toxicity compared to HBOT at one and two months follow-up ($p<0.05$). At three months follow-up tissue toxicity had reduced in both groups and the difference between the groups was no longer statistically significant ($p>0.05$). By three months tissue toxicity had reduced from 12.2 ± 2.9 to 4.8 ± 3.5 in the HBOT group and had reduced from 13.3 ± 2.9 to 3.0 ± 3.5 in the APC group.

Safety

Only one study provided statistical analysis comparing adverse events between their two groups (Shao et al 2011). This study only reported incidence of urinary tract infection (UTI) which was significantly higher in the HA group than the HBOT group at six months follow-up (43% vs 10%, $p=0.03$). At 12 and 18 months follow-up there was no statistically significant difference in UTI between the groups ($p=0.1$). At final follow-up at 18 months the proportion of UTIs was 50% for the HA group and 30% for the HBOT group.

Two studies reported the proportion of adverse events for each of their groups but did not report any statistical analysis comparing safety outcomes for the two groups (Glover et al 2016; Álvaro-Villegas et al 2011). Glover et al (2016) reported six serious adverse events in six HBOT patients and two serious adverse events in two sham patients but did not consider that any of these related to treatment. Common adverse events reported by Glover et al included eye refractive changes including myopia affecting about 30% of the HBOT group and 11% of the sham group; increased fatigue or tiredness affecting 4% of the HBOT group and 11% of the sham group; and ear pain or barotrauma affecting 28% of the HBOT group and 21% of the sham group. Two patients in Glover et al stopped treatment due to anxiety (group not specified). Adverse events reported by Álvaro-Villegas et al (2011) for the APC group included APC-related rectal ulcers (21%), rectal pain (14%) and persistent rectal bleeding (21%). For the HBOT group only persistent rectal bleeding was reported affecting 18% of the group.

Clarke et al reported adverse events for the whole study population but did not specify treatment group. Adverse events experienced included ear pain or discomfort (16%), transient myopia (3%) and confinement anxiety (2%).

2. Is there evidence that the effect of adjunct HBOT differs in the following three sub-groups:

a) In patients in whom there is no evidence of cancer recurrence?

Evidence of or history of cancer recurrence was an exclusion criteria for the Glover et al (2016) RCT. Therefore their study population provides evidence for the effectiveness of HBOT in patients in whom there is no evidence of cancer recurrence. In Glover et al's study there was no significant difference between HBOT and sham for any of the outcomes assessed. These outcomes included gastrointestinal symptoms, rectal bleeding and bowel dysfunction.

Descriptive results for a subset of patients who experienced cancer recurrence during a study are discussed in response to the next question.

b) In patients who are treated in palliative circumstances, in the presence of tumour recurrence, for control of genitourinary and/or gastrointestinal symptoms?
None of the included studies specifically recruited patients who were in palliative circumstances or had tumour recurrence. However Clarke et al (2008) provided a descriptive summary of outcomes for 14 patients within their study population who experienced cancer recurrence during the treatment or follow-up phase (five years). This noted that approximately 45% of patients who did not show a treatment response were diagnosed with local recurrence. Clarke et al also noted that the LENT SOMA scores of these patients deteriorated by an average of nine points (range 4 to 17) by the time the cancer was diagnosed. These results are from a description of a subset of patients who took part in an RCT. This was not a formal subgroup within the study and no statistical analysis was performed.

All of the included studies recruited patients with genitourinary and/or gastrointestinal symptoms as specified in the PICO. The results of the studies described in response to question one therefore apply to this subgroup. The included studies do not support a comparison of the evidence for patients with different symptoms prior to receiving HBOT due to differences in the outcome measures reported over different time periods.

c) In patients who receive 30 or more hyperbaric oxygen treatments?
The protocols for all of the included studies involved 30 or more hyperbaric oxygen treatments. The results of the studies described in response to question one therefore apply to this subgroup. The studies did not report separate analyses based on the number of HBOT treatments received.

3. What evidence is there that any effects are sustained in the medium and longer term?
The follow-up period varied between the studies with three of the four studies following patients for at least 12 months. However Glover et al (2016) only reported outcomes at one time period (12 months) and did not find any significant benefit for HBOT compared to sham treatment.

Clarke et al (2008) had the longest follow-up period of up to five years. The improvement in mean LENT SOMA score from baseline and the proportion of patients showing at least some improvement on clinical evaluation appeared to be sustained during the follow-up period. However the number of patients participating in follow-up assessment dropped steeply over the study period with, for example, 105 patients at 12 months, 61 patients at two years and 14 patients at five years. As this was a crossover trial it was not possible to assess longer term differences between groups.

Shao et al (2011) followed patients up for 18 months. In their study the proportion of patients showing a complete or partial response to treatment decreased over the 18 month period. For example, the proportion showing a complete response was 75% and 88% in the HBOT and HA groups respectively at six months and approximately 50% in both groups at 18 months.

Cost effectiveness

4. What is the cost effectiveness of HBOT for the treatment of soft tissue radiation damage?
No studies assessing the cost effectiveness of HBOT for soft tissue radiation damage were identified.

5 Discussion

Two well-designed double-blind RCTs have compared HBOT to sham. One of these trials (Glover et al 2016) reported direct comparisons of HBOT to sham at 12 months follow-up and found no significant differences between the two groups for outcomes of rectal bleeding, gastrointestinal symptoms and bowel dysfunction. The other crossover trial only reported statistical analysis for outcomes immediately following treatment (Clarke et al 2008). In direct comparisons between the groups this trial reported statistically significantly better outcomes for HBOT compared to sham for mean LENT SOMA score and the proportion of patients showing at least some improvement on clinical evaluation.

There were limitations in both of these trials, particularly relating to the analyses and scoring of outcome measures. The primary results reported for these studies were not based on intention-to-treat analyses with both studies excluding patients from the analyses due to missing data and/or failure to adhere to treatment protocols. For example, the primary analysis reported by Glover et al is based on 69 patients of 84 randomised and the primary analysis reported by Clarke et al is based on 120 patients of 150 randomised. The power calculation for Glover et al required 75 evaluable patients suggesting that this study may have been underpowered to detect changes. No power calculation was reported by Clarke et al.

Direct comparison between the studies is not possible due to the different outcome measures reported and the different time periods used for the assessment of outcomes following treatment. However, Glover et al did describe an exploratory analysis conducted at two weeks post-treatment that did not show any difference between their HBOT and sham groups. No numerical or statistical details were provided for this time period.

It is difficult to interpret the clinical meaningfulness of some of the statistically significant results observed due to a lack of detail in the reporting of the outcome measures used.

Two studies comparing HBOT to other treatments were also identified. The results of these studies generally showed no statistical difference between the two study groups or favoured the alternative treatment of either hyaluronic acid instillation (Shao et al 2011) or argon plasma coagulation (Álvaro-Villegas et al (2011). These were small, single-centre studies, only one of which (Shao et al) randomised patients into treatment groups. It was not clear what alternative treatments had been received prior to recruitment into the study.

The included studies do not support a comparison of the evidence for patients presenting with different symptoms prior to receiving HBOT due to differences in the outcome measures reported over different time periods.

Given the discrepancy in the results of the two sham-controlled trials identified and the limitations of these studies, further adequately powered trials comparing HBOT to sham may be warranted.

6 Conclusion

The evidence identified for HBOT for the treatment of soft tissue radiation damage after pelvic irradiation included three randomised controlled trials and one non-randomised controlled study. Studies reported improvements from baseline following HBOT treatment. However, only one of the two studies comparing HBOT to sham provides evidence of better outcomes with HBOT treatment. This was the largest study identified, but only reported comparative outcomes immediately following treatment and the clinical meaningfulness of the improvements observed with HBOT is unclear.

Two small studies comparing HBOT to other treatments also showed improvement with HBOT but HBOT was not superior to the alternative treatments.

At present there is inconsistent evidence about the efficacy of HBOT compared to sham in the treatment of soft tissue radiation damage following pelvic irradiation. HBOT was not superior to alternative treatments in two small studies.

7 Evidence Summary Table

For abbreviations see list after each table

Use of HBOT Vs. Sham Treatment to Treat Soft Tissue Radiation Damage After Pelvic Irradiation									
Study reference	**Study design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of evidence score**	**Applicability**	**Critical appraisal summary**
Glover et al 2016	P1 - Randomised double-blind, sham controlled phase 3 trial 10 UK centres	Patients (≥18 years) with chronic adverse effects of curative pelvic radiotherapy after ≥3 months of unsuccessful optimal medical therapy (n = 84) Randomised into: HBOT n = 55 Sham n = 29 Patients had ≥ grade 2 gastrointestinal symptoms in any LENT SOMA category for radiation injury or grade 1 gastrointestinal symptoms with intermittent symptoms attributed to radiotherapy for carcinoma of the rectum, prostate, testis, bladder, uterine cervix, uterine corpus, vagina, vulva or ovary for ≥ 12 months before	Intervention group: 40 HBOT treatments at 2.4 ATA (243 kPa) for 90 minutes, once daily, 5 days per week Sham group: 40 sham pressure exposures of air at 1.3 ATA (131 kPa) for 90 minutes, once daily, 5 days per week Randomisation (2:1) by computer-generated random permuted blocks of 9 or 12 with stratification by centre Patients and health-care professionals blinded to study group	Primary Clinical effectiveness	Change in gastrointestinal symptoms score on IBDQ	**Median (IQR) score at baseline** HBOT: 48 (42 to 52) Sham: 51 (44 to 59) **Median (IQR) change in overall bowel function from baseline to 12 months follow-up** HBOT: 3.5 (-3 to 11) Sham: 4 (-6 to 9) A positive median change represents an improvement in score No significant difference between groups (p=0.50) Reported sensitivity analysis included all data returned at 12 months follow-up and a per-protocol analysis. For all data returned for the 12-month timepoint irrespective of time of return, the difference in change from baseline to 12 months between the 2 study groups was consistent with the modified intention to treat analysis (p=0.48). For the per protocol analysis p=0.35. Exploratory analysis at 2-weeks post-treatment showed no difference between groups	9 /10	Direct	The authors describe a modified intention to treat population based on the return of data forms within specified time periods and including 74 patients (26 sham, 48 HBOT). However only 69 patients are included in the analysis of the primary outcome of change in gastrointestinal symptoms and 40 patients in the change in rectal bleeding score. This includes the further exclusion of patients who had IBDQ bowel component or rectal bleeding scores missing at baseline or 12 month follow-up. The power calculation for this study required 75 evaluable patients. The study was therefore underpowered to detect the expected minimum change in the primary outcome of change in gastrointestinal symptoms. An analysis of all patients who returned IBDQ forms regardless of timelines was conducted as a planned sensitivity analysis. The authors also conducted per-protocol analysis (n=60) which excluded patients who did not return data forms (n=10), patients who did not receive at least 32 exposures within a 10 week period (n=9) and patients with missing IBDQ bowel component scores (n=5). The population for safety outcomes included 81 patients who received at least one exposure (28 sham, 53 HBOT).
				Primary Clinical effectiveness	Change in rectal bleeding score on IBDQ	**Median (IQR) score at baseline** HBOT: 3 (2 to 4) Sham: 3 (2 to 4)			

		enrolment Patients with evidence or history of cancer recurrence were excluded				**Median (IQR) change in rectal bleeding from baseline to 12 months** HBOT: 3 (1 to 3) Sham: 1 (1 to 2) A positive median change represents an improvement in score No significant difference between groups (p=0.09) Reported sensitivity analysis included all data returned at 12 months follow-up and a per-protocol analysis. For all data returned for the 12-month timepoint irrespective of time of return, the difference in change from baseline to 12 months between the 2 study groups was consistent with the modified intention to treat analysis (p=0.04). For the per protocol analysis p=0.15. Exploratory analysis at 2-weeks post-treatment showed no difference between groups			The authors did not fully report the results of two of the planned secondary outcomes. For one of these (clinical assessment of gastrointestinal symptoms on CTCAE) the authors stated that there was no difference between the groups but no numerical values were reported. For the other secondary outcome (quality of life) the authors stated that this outcome was not reported because the negative results of the CTCAE descriptive analysis meant that analysis of these data could not affect the interpretation or conclusions of the trial. Patients were assessed at baseline, 2 weeks after treatment and at 3, 6, 9 and 12 months follow-up. No results are reported for 3, 6 or 9 months follow-up. Some details of exploratory analysis conducted on the 2 week data are reported.
				Secondary Clinical effectiveness	Change in adverse effects (bowel dysfunction) on LENT SOMA	**Median (IQR) rectal score at baseline** HBOT: 6 (4 to 8) Sham: 6 (5 to 8) **Median (IQR) change in LENT SOMA rectal from baseline to 12 months** HBOT: -1 (-2 to 1) Sham: -1.5 (-4 to 0) A negative median change represents an improvement in score No significant difference between groups (p=0.12) Sensitivity analysis including all data returned at 12 months follow-up irrespective of timelines were reported to give similar results. For all data returned for the 12-month timepoint irrespective of			

						time of return p=0.11. Per protocol analysis for this outcome not reported **Median (IQR) intestine score at baseline** HBOT: 4 (2 to 5) Sham: 2.5 (1 to 4) **Median (IQR) change in LENT SOMA intestine from baseline to 12 months** HBOT: 0 (-2 to 0) Sham: 0 (-1 to 1) A negative median change represents an improvement in score No significant difference between groups (p=0.20) Sensitivity analysis including all data returned at 12 months follow-up irrespective of timelines were reported to give similar results For all data returned for the 12-month timepoint irrespective of time of return p=0.16. Per protocol analysis for this outcome not reported Exploratory analysis at 2-weeks post-treatment showed no difference between groups			
				Safety	Adverse events	**Serious Adverse Events (SAE)** HBOT (n=6 in 6 patients): • Malignancy requiring surgery (n=2) • Recurrence of vomiting and dehydration (n=1) • Diarrhoea and fever associated with Campylobacter infection (n=1) • Recurrence of abdominal pain, bloating, diarrhoea and UTI (n=1) • Aneurysm (n=1) Sham (n=2 in 2 patients): • Tonsillitis requiring surgery (n=1)			

						• Recurrent cancer of the vulva (n=1) No SAE were considered treatment related **Common Adverse Events** **Eye refractive changes including myopia** HBOT: 30.2% (16/53) Sham: 10.7% (3/28) **Increased fatigue or tiredness** HBOT: 3.8% (2/53) Sham: 10.7% (3/28) **Ear pain or barotrauma** HBOT: 28.3% (15/53) Sham: 21.4% (6/28) 2 patients stopped treatment early due to anxiety No statistical tests reported for safety outcomes			
Clarke et al 2008	P1 - Randomised double-blind, sham controlled crossover trial 5 centres in Mexico (1), South Africa (1), Turkey (1) and Australia (2)	Patients with rectal late radiation tissue injury following pelvic radiotherapy with diagnosis present for ≥3 months and insufficient response to other therapies (n = 150) Randomised into: HBOT n = 75 Sham n = 75 Patient grade of symptoms at baseline not reported as an inclusion criteria.	Intervention group: 30 HBOT treatments at 2.0 ATA (203 kPa) for 90 minutes, once daily, 5 days per week Sham group: 30 sham pressure exposures of air at 1.1 ATA (111 kPa) for 90 minutes, once daily, 5 days per week Randomisation sequence (1:1) generated by	Primary Clinical effectiveness	Change in LENT SOMA score	**Mean LENT SOMA at baseline** HBOT: 12.55 Sham: 12.84 **Change in mean LENT SOMA from baseline to immediately post treatment** HBOT: 5.00 (95%CI 3.96 to 6.03) Sham: 2.61 (95%CI 1.51 to 3.70) Statistically significant improvement from baseline for both groups (p<0.0001) Improvement statistically significantly greater in HBOT than sham (p=0.0019) Statistically significant lower average scores for HBOT than sham (p=0.0150). This is reported as an estimated difference of 1.93	8 /10	Direct	120 of the 150 patients enrolled completed the study protocol. Analyses are based on the 120 patients for which data were available. No power calculation was reported. Of the 30 patients who did not complete the study, 11 were from the HBOT group and 19 from the sham group. Reasons for drop out were provided by the study authors and included: • Patients underwent definitive surgery • Patients lost before starting the study • Tumour activity/ recurrence • Ill health • Socio-economic reasons • Refusal to start treatments. Three intention-to-treat analysis scenarios[2] were considered for the clinical evaluation outcome.

[2] Three scenarios were considered: all those for whom no results were available had had improvement; all those for whom no results were available had not had improvement; for each patient type, half of those for whom no results were available had had improvement and half had no improvement

		Presenting symptoms are listed by individual patient and suggest the majority were experiencing haemorrhage	biostatisticians and used a blocking process with block size of 4 Patients reassessed after 30 treatment sessions by a blinded assessor. 10 additional treatment sessions were given to selected patients depending on individual response Sham patients were offered crossover to active treatment after completion of the sham treatment. Three patients did not accept crossover treatment Patients and health-care professionals blinded to study group			(95%CI 0.38 to 3.48) **Mean LENT SOMA scores at follow-up** After crossover no significant differences in LENT SOMA score between groups (p=0.66) At 3 months (n=103) HBOT: 5.96 Sham/HBOT: 7.17 At 6 months (n=103) HBOT: 6.85 Sham/HBOT: 7.31 At 1 year (n=105) HBOT: 5.29 Sham/HBOT: 6.72 At 2 years (n=61) HBOT: 3.61 Sham/HBOT: 6.20 At 3 years (n=38) HBOT: 3.55 Sham/HBOT: 3.89 At 4 years (n=29) HBOT: 4.21 Sham/HBOT: 4.00 At 5 years (n=14) HBOT: 3.71 Sham/HBOT: 4.29 No statistical tests reported for outcomes at follow-up **Cancer recurrence** The LENT SOMA scores of 14 patients with cancer recurrence during the treatment or follow-up phase deteriorated by an average of 9 points (range 4 to 17) by the time the recurrence was diagnosed. Approximately 45% of patients without a treatment response were diagnosed with local recurrence			Of the 120 patients who completed the allocated intervention, 103 completed follow-up at 3 and 6 months. Follow-up at 1, 2, 3, 4 and 5 years was completed by 105, 61, 38, 29 and 14 patients respectively. It is not clear exactly when the post treatment outcomes were assessed. Limited details are provided about the scoring of the LENT SOMA scale and the severity of patient's symptoms. No definition of a clinically meaningful result is provided. The primary analysis of change in LENT SOMA compared improvement from baseline. A comparison between the groups is reported based on an estimated difference. It is not clear why an estimated difference is used for this comparison. No statistical analysis reported for the longer term follow-up results. The analysis of the LENT SOMA and QoL scores was adjusted for covariates which included gender, tobacco use, external beam radiotherapy and brachytherapy, interval between radiotherapy and symptoms, interval between symptoms and treatment and county of residence. Some confidence intervals were wide, reducing confidence in the result.

				Primary Clinical effectiveness	Clinical evaluation (healed; significant improvement; moderate improvement; no improvement)	**Proportion of patients with at least some improvement immediately post treatment:** HBOT: 88.9% (56/63) Sham: 62.5% (35/56) The proportion of patients showing at least some improvement was statistically significantly greater for HBOT than sham (p=0.0009). OR 5.93 (95%CI 2.04 to 17.24) Three intention-to-treat analysis scenarios (see critical appraisal summary) found that the proportion of patients showing improvement was statistically significantly greater for HBOT than sham (p<0.005) The proportion of patients in each category immediately post treatment was: *Healed* HBOT: 7.9% (5/63) Sham: 0% (0/56) *Significant improvement* HBOT: 38.1% (24/63) Sham: 26.8% (15/56) *Moderate improvement* HBOT: 42.9% (27/63) Sham: 35.7% (20/56) *No improvement* HBOT: 11.1% (7/63) Sham: 37.5% (21/56) **Proportion of patients with at least some improvement at follow-up:** After crossover 88.7% (47/53) of the sham/HBOT group showed some improvement At 3 months (n=103) HBOT: 65.5% (36/55) Sham/HBOT: 58.3% (28/48)			

						At 6 months (n=103) HBOT: 61.8% (34/55) Sham/HBOT: 56.3% (27/48) At 1 year (n=105) HBOT: 67.3% (37/55) Sham/HBOT: 64.0% (32/50) At 2 years (n=61) HBOT: 75.0% (27/36) Sham/HBOT: 52.0% (13/25) At 3 years (n=38) HBOT: 85.0% (17/20) Sham/HBOT: 83.3% (15/18) At 4 years (n=29) HBOT: 100% (14/14) Sham/HBOT: 80% (12/15) At 5 years (n=13) HBOT: 83.3% (5/6) Sham/HBOT: 85.7% (6/7) No statistical tests reported for outcomes at follow-up			
				Secondary Clinical effectiveness	Change in quality of life (QoL) using bowel bother and bowel function subscales of the EPCICBD and SF-12 to assess general wellbeing	**Mean bowel-specific QoL scores at baseline** Bowel bother • HBOT: 45% • Sham: 53% Bowel function • HBOT: 60% • Sham: 61% **Change in bowel-specific QoL from baseline to immediately post treatment:** HBOT: • Bowel bother 14% • Bowel function 9% Sham: • Bowel bother 5% • Bowel function 6% The improvement in bowel bother score from baseline was statistically significant for HBOT (p=0.0007) but not for sham (p=0.1521)			

						No statistical analysis results were reported for bowel function No statistical analyses comparing HBOT to sham were reported No differences were observed in general wellbeing(no numerical figures reported) **QoL at follow-up:** After crossover, the sham group showed an improvement of 14% for bowel bother and 10% for bowel function. The improvement for bowel bother was statistically significant (p=0.0002) QoL scores assessed at 3 and 6 months and 1 to 5 years For the HBOT group these range from 58% (at 3 months) to 89% (at 5 years) For the sham/ HBOT crossover group these range from 69% (at 5 years) to 80% (at 3 months) No statistical tests were reported for outcomes at follow-up			
				Safety	Adverse events	**Adverse events** • Ear pain or discomfort: 15.8% (19/120) • Transient myopia: 3.3% (4/120) • Confinement anxiety: 1.7% (2/120)			

ATA – Atmospheres of Absolute Pressure; CI – Confidence Interval; CTCAE – Common Terminology Criteria for Adverse Events gastrointestinal scale (version 4); EORTC – European Organisation for Research and Treatment of Cancer; EPCICBD – Expanded Prostate Cancer Index Composite Bowel Domain; HBOT – Hyperbaric Oxygen Therapy; IBDQ – modified Inflammatory Bowel Disease Questionnaire; IQR – Interquartile Range; kPa – Kilopascal; LENT SOMA – Late Effects in Normal Tissues Subjective, Objective, Management and Analytic; QLQ-C30 – C30 core quality of life questionnaire; OR – Odds Ratio; QLQ-CR38 – CR38 colorectal module; QoL – Quality of Life; SAE – Serious Adverse Events; SF-12 – Short Form General Health Function Survey; UTI – Urinary Tract Infection

Use of HBOT Vs. Intravesical Hyaluronic Acid Instillation to Treat Soft Tissue Radiation Damage After Pelvic Irradiation									
Study reference	**Study design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of evidence score**	**Applicability**	**Critical appraisal summary**
Shao et al 2011	P1 - Randomised controlled trial 1 centre in China	Patients with haemorrhagic cystitis after radiotherapy for pelvic cancers (including cervical cancer, rectal cancer and prostate cancer) (n=36) Randomised into HBOT: n=20 Hyaluronic acid (HA): n=16 Patients had grade II or III haemorrhagic cystitis at baseline[3] 6 patients had received bladder irrigation prior to HBOT (3 patients in each group). No other	Group 1: 30 HBOT treatments at 2.5 ATA (253kPa) for 60 minutes, once a day, 7 days a week Group 2: 40mg of HA instilled into the bladder, weekly for 1 month then monthly for 2 months Randomisation by computer-generated random numbers	Primary Clinical effectiveness	Improvement in symptoms (complete response = all symptoms disappeared; partial response = disappearance of clots but persistence of macroscopic haematuria)	**Proportion of patients with partial or complete response (CR)** At 6 months HBOT: 95% (19/20, including 15/20 CR) HA: 100% (16/16, including 14/16 CR) At 12 months HBOT: 85% (17/20, including 10/20 CR) HA: 94% (15/16, including 12/16 CR) At 18 months HBOT: 75% (15/20, including 9/20 CR) HA: 75% (12/16, including 8/16 CR) No statistically significant differences between groups at any follow-up point (p>0.05)	8 /10	Direct	All 36 patients completed the study and were included in the analysis. The authors did not report any blinding of assessors. Limited detail was provided on the randomisation process. This was a single centre trial with a small number of patients. The HBOT group received treatments 7 days a week. It is not clear how long patients had symptoms for or what alternative treatments had been tried prior to recruitment in the trial.
				Primary Clinical effectiveness	Change in voiding frequency (mean± SD)	**Baseline number of voids per day** HBOT: 9.8 ± 1.7 HA: 10.4 ± 1.8 **Change in number of voids per day** At 6 months HBOT: -1.2 ± 1.1 HA: -2.9 ± 1.7			

[3] Haemorrhagic cystitis was graded as follows: grade I microscopic haematuria; grade II macroscopic haematuria; grade III macroscopic haematuria with the presence of clots and/or decrease in haemoglobin levels necessitating blood transfusions; grade IV life-threatening bleeding not responding to treatment and necessitating surgical intervention (Shao et al 2011)

		details of prior treatments were reported Patients who received radiotherapy for bladder cancer were excluded				At 12 months HBOT: -0.2 ± 1.0 HA: -1.5 ± 1.4 At 18 months HBOT: 0.2 ± 0.8 HA: -0.2 ± 0.5 The improvement in voiding frequency from baseline was statistically significant in both groups at 6 months (p<0.01) and in the HA group at 12 months (p<0.01) No direct comparison between groups was reported for this outcome			
				Primary Clinical effectiveness	Change in pelvic pain on VAS (mean± SD)	**Baseline VAS** HBOT: 2.5 ± 2.2 HA: 2.8 ± 2.2 **Change in VAS** At 6 months HBOT: -0.9 ± 0.8 HA: -0.9 ± 1.4 At 12 months HBOT: -0.9 ± 1.0 HA: -1.3 ± 1.3 At 18 months HBOT: -1.2 ± 1.2 HA: -1.5 ± 1.2 The improvement in VAS from baseline was statistically significant in both groups at all follow-up points (p<0.05) No direct comparison between groups was reported for this outcome			
				Safety	Adverse events	**Incidence of urinary tract infection** At 6 months HBOT: 10% HA: 43% At 12 months HBOT: 25% HA: 50%			

						At 18 months HBOT: 30% HA: 50% The incidence of urinary tract infection was statistically significantly higher for HA than HBOT at 6 months (p=0.03). There was no significant difference between the groups at other time points (p=0.1)			

ATA – Atmospheres of Absolute Pressure; CR – Complete Response; HA – Hyaluronic acid; HBOT – Hyperbaric Oxygen Therapy; kPa – Kilopascal; VAS – Visual Analogue Scale

Use of HBOT Vs. Argon Plasma Coagulation to Treat Soft Tissue Radiation Damage After Pelvic Irradiation									
Study reference	**Study design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of evidence score**	**Applicability**	**Critical appraisal summary**
Álvaro-Villegas et al 2011	P1 – non-randomised controlled study 1 centre in Mexico	Patients with chronic radiation proctopathy and grade 4[4] rectal bleeding secondary to radiotherapy for cervical cancer (n=31) Treatment groups HBOT: 17 Argon plasma coagulation (APC): 14 Mean (SD) duration of bleeding at baseline (months) HBOT: 7.8 (4.7) APC: 9.6 (5.1)	Group 1: ≥30 HBOT treatments at 2-2.5 AKA (203-253 kPa) for 90 minutes. Number of treatments per day or week not reported Group 2: APC non- contact coagulation applied to all endoscopically visible abnormal mucosa No randomisation performed. Patients referred by primary care physician according to resource availability at the time of referral	Primary Clinical effectiveness	Haemoglobin level (mean ± SD)	**At baseline** HBOT: 10.3 ± 2.6 APC: 10.1 ± 2.1 **At 1 month follow-up** HBOT: 10.7 ± 2.5 APC: 11.2 ± 2.0 **At 2 months follow-up** HBOT: 11.0 ± 2.6 APC: 11.6 ± 1.7 **At 3 months follow-up** HBOT: 12.0 ± 2.1 APC: 11.3 ± 2.0 No significant difference between groups at any follow-up point (p>0.05)	6 /10	Direct	It is not clear if all patients completed all follow-up points although no loss to follow-up was reported. Only one-tailed ANOVA results were reported. This was a single centre study with a small number of patients. Patients were not randomised into the treatment groups. Patient group was determined by resource availability. The authors state that duration or severity of bleeding was not a factor in referral to treatment group and there were no significant differences between the groups at baseline. The authors did not report any blinding of assessors. Patients had severe symptoms at baseline (haemorrhage requiring transfusion). It is not clear what other treatments were received before HBOT.
				Primary Clinical effectiveness	Number of transfusions (mean ± SD)	**At baseline** HBOT: 3.8 ± 2.9 APC: 4.8 ± 7.8 **At 1 month follow-up** HBOT: 3.4 ± 3.9 APC: 0.6 ± 1.1 **At 2 months follow-up** HBOT: 2.5 ± 3.0 APC: 0.7 ± 1.3 **At 3 months follow-up** HBOT: 0.8 ± 1.2 APC: 0.6 ± 0.9 APC statistically significantly better outcome at 1 month			

[4] Rectal bleeding was assessed on the Chutkan Scale (grade 0 – no haemorrhage; grade 1 – blood on toilet paper or mixed with faeces; grade 2 – drops of blood in the toilet; grade 3 – severe haemorrhage with expulsion of clots; grade 4 – haemorrhage which requires transfusion)

						and 2 months (p<0.05). No significant difference between groups at 3 months			
				Primary Clinical effectiveness	Tissue toxicity LENT SOMA score (mean ± SD)	**At baseline** HBOT: 12.2 ± 2.9 APC: 13.3 ± 2.9 **At 1 month follow-up** HBOT: 8.6 ± 3.7 APC: 5.3 ± 3.4 **At 2 months follow-up** HBOT: 7.2 ± 4.8 APC: 3.8 ± 2.9 **At 3 months follow-up** HBOT: 4.8 ± 3.5 APC: 3.0 ± 3.5 APC statistically significantly better outcome at 1 month and 2 months (p<0.05). No significant difference between groups at 3 months			
				Safety	Adverse events	**APC group** APC-associated rectal ulcers: 21.4% (3/14) Rectal pain: 14.3% (2/14) Persistent rectal bleeding: 21.4% (2/14) **HBOT group** Persistent rectal bleeding: 17.6% (3/17)			

APC – Argon Plasma Coagulation; ATA – Atmospheres of Absolute Pressure; HBOT – Hyperbaric Oxygen Therapy; kPa – Kilopascal; LENT SOMA – Late Effects in Normal Tissues Subjective, Objective, Management and Analytic ; SD – standard deviation

8 Grade of evidence table (for abbreviations see list after each table)

Use of HBOT Vs. Sham Treatment to Treat Soft Tissue Radiation Damage After Pelvic Irradiation					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Change in gastrointestinal symptoms	Glover et al 2016	9 /10	Direct	B	Change in gastrointestinal symptoms was assessed using 10 questions on the modified Inflammatory Bowel Disease Questionnaire (IBDQ). Each question was graded on a scale of 1 (more than ever before) to 7 (normal/ not at all).This would give a summed score of between 10 (most severe) and 70 (least severe). An improvement of 7 (SD 10) from baseline to 12 month follow-up was considered clinically relevant. An improvement in median change from baseline IBDQ score for gastrointestinal symptoms was seen in both the HBOT (by 3.5 points) and sham groups (by 4 points). However, there was no significant difference between the group receiving HBOT and the group receiving sham at 12 months follow-up (p=0.50). An exploratory analysis at 2-weeks post treatment also found no difference between the groups. No analysis on change from baseline was reported. There was no difference in the improvement seen with HBOT compared with sham treatment and the size of the improvement seen in both groups was less than the 7 point improvement that would be considered clinically relevant. This was a well-designed, double-blind, sham-controlled RCT. However, the primary analyses reported in this study did not include all patients and not all results were reported. The analysis of gastrointestinal symptoms included 69 of the 84 patients recruited to the trial. The study may have been underpowered to detect changes.
Change in rectal bleeding	Glover et al 2016	9 /10	Direct	B	Change in rectal bleeding was assessed using a single question on the IBDQ (“have you had a problem with bleeding from your bottom?”). This question was graded on a scale of 1 (more than ever before) to 7 (normal/ not at all). An improvement in median change from baseline IBDQ score for rectal bleeding was seen in both the HBOT (by 3 points) and sham groups (by 1 point). However, there was no significant difference between the group receiving HBOT and the group receiving sham at 12 months follow-up (p=0.09). An exploratory analysis at 2-weeks post treatment also found no difference between the groups. No analysis on change from baseline was reported. There was no significant difference in the improvement seen with HBOT or sham treatment. This was a well-designed, double-blind, sham-controlled RCT. However, the primary analyses reported in this study did not include all patients and not all results were reported. The analysis of rectal bleeding included 40 of the 84 patients recruited to the trial. The study may have been underpowered to detect changes.

Change in mean LENT SOMA score	Clarke et al 2008	8 /10	Direct	B	The LENT SOMA scale is an anatomic-specific morbidity scoring system for severity of radiation-induced complications. Symptoms are scored from grade I (least severe) to grade 4 (most severe). There are 14 parameters within the subjective (5), objective (3) and management (6) sections plus an analytic section which includes 6 tests (e.g. MRI and ultrasound) but is not scored. The authors describe a first 'LENT score' as being the sum of the scores for the 14 parameters in the subjective, objective and management sections and a second 'LENT score' as being the summed score divided by 14. It is likely that it is the second LENT score is that is used for the mean LENT SOMA scores presented in the study however this is not clearly stated. A statistically significant improvement in mean score from baseline was reported for both the HBOT (5.00 95%CI 3.96 to 6.03) and sham groups (2.61 95%CI 1.51 to 3.70) ($p<0.0001$) immediately after treatment. At baseline the scores were 12.55 and 12.84 for HBOT and sham respectively. The improvement for HBOT was reported as significantly greater than for sham ($p=0.0019$). A direct comparison between the groups reported a significantly lower average score for HBOT than sham ($p=0.0150$), however this was based on an estimated difference. It is not clear why an estimated difference was used. The mean scores of the sham group improved after the crossover to HBOT treatment. The improvement in mean LENT SOMA scores appeared to be sustained during the 5 year follow-up period, however the number of patients providing follow-up data dropped steeply after 1 year. As this was a crossover trial it is not possible to assess longer term differences between the treatment groups. This was a well-designed, double-blind, sham-controlled RCT. However, the primary analyses reported in this study only included 120 of the 150 patients recruited. Limited information about the severity of patients' symptoms makes it difficult to interpret the clinical significance of the results.
Improvement on clinical evaluation	Clarke et al 2008	8 /10	Direct	B	Clinical evaluation was assessed as healed, significant improvement, moderate improvement or no improvement. No further definition of these categories was provided. A greater proportion of HBOT patients showed at least some improvement (i.e. healed, significant or moderate) than patients receiving sham treatment (88.9% vs 62.5%) ($p=0.0009$; OR 5.93 95%CI 2.04 to 17.24). The proportion of patients considered healed was 7.9% for HBOT and 0% for sham. In contrast the proportion of patients with no improvement was 11.1% for HBOT and 37.5% for sham. No significance tests were reported for individual clinical evaluation categories. This was a well-designed, double-blind, sham-controlled RCT. However, the primary analyses reported in this study only included 120 of the 150 patients recruited. A greater proportion of patients showed improvement with HBOT but only 7.9% (5/63) were considered healed. No definition was provided for significant or moderate improvement so the clinical significance of these results is not clear.

Change in bowel dysfunction (assessed using LENT SOMA)	Glover et al 2016	9 /10	Direct	B	Bowel dysfunction was assessed using the rectal and intestine scales of LENT SOMA. The rectal scale includes 5 questions with a summed score range of 0 (no symptoms) to 20 (worst possible symptoms). The intestine scale includes 4 questions with a summed score range of 0 (no symptoms) to 15 (worst possible symptoms). An improvement in median change from baseline on the LENT SOMA rectal score was seen in both the HBOT (by 1 point) and sham groups (by 1.5 points) at 12 months follow-up. There was no median change from baseline for either the HBOT or sham group on the LENT SOMA intestine score. There was no significant difference between the HBOT and sham groups at 12 months follow-up for rectal score (p=0.12) or intestine score (p=0.20). An exploratory analysis at 2-weeks post treatment also found no difference between the groups. No analysis of change from baseline was reported. This was a well-designed, double-blind, sham-controlled RCT. However, the primary analyses reported in this study did not include all patients and not all results were reported. It is not clear how many patients were included in this analysis. The study may have been underpowered to detect changes.
Quality of life	Clarke et al 2008	8 /10	Direct	B	Quality of life measurements were taken from surveys including the bowel function and bowel bother subscales of the Expanded Prostate Cancer Index Composite Bowel Domain and the SF-12 General Health Function survey. The bowel bother and bowel function scales are reported as a percentage (i.e. a 0-100 scale) with higher scores representing better quality of life. The authors reported that no differences were observed in general well-being, however no results or analysis of the SF-12 were reported. Both groups showed an improvement in mean bowel bother and bowel function scores from baseline to immediately following treatment. A greater, and statistically significant improvement from baseline was reported for the bowel bother score (p=0.0007) for the HBOT group but not for the sham group (p=0.1521). However, the score for the HBOT group was lower at baseline and the scores immediately following treatment were similar for both groups. No direct comparison of the scores between groups was reported. No statistical analysis for bowel function was reported. The improvement in mean bowel bother and bowel function scores appeared to be sustained during the 5 year follow-up period, however the number of patients providing follow-up data dropped steeply after 1 year. As this was a crossover trial it is not possible to assess longer term differences between the treatment groups. The results available do not suggest that there was any meaningful difference in quality of life between the HBOT and sham groups following treatment. This was a well-designed, double-blind, sham-controlled RCT. However, the primary analyses reported in this study only included 120 of the 150 patients recruited and not all results are reported.

Safety	Glover et al 2016	9 /10	Direct	A	Neither study reported any statistical analysis on differences in safety outcomes between HBOT and sham. Only Glover et al (2016) reported safety outcomes by treatment group. Glover et al (2016) reported 8 serious adverse events in 8 patients (6 HBOT and 2 sham) but did not consider any of these to be treatment related. Common adverse events were reported by Glover et al (2016). The proportion of patients reporting eye refractive changes (including myopia) and ear pain or barotrauma was higher in the HBOT group (30.2% and 28.3%) than in the sham group (10.7% and 21.4%). A higher proportion of patients reported increased fatigue or tiredness in the sham group (10.7%) than the HBOT group (3.8%). Differences were reported between the HBOT and sham groups in the proportion of patients reporting eye refractive changes, ear pain, barotrauma, and fatigue or tiredness. However, it is not clear if these differences were statistically significant. In the absence of significance tests or further details on the seriousness or impact of the common adverse event s observed (e.g. treatment required) the clinical significance is not clear.
	Clarke et al 2008	8 /10	Direct		

CI – Confidence Interval; HBOT – Hyperbaric Oxygen Therapy; IBDQ – modified Inflammatory Bowel Disease Questionnaire; IQR – Interquartile Range; LENT SOMA – Late Effects in Normal Tissues Subjective, Objective, Management and Analytic; OR – Odds Ratio. RCT – Randomised Controlled Trial

Use of HBOT Vs. Intravesical Hyaluronic Acid Instillation to Treat Soft Tissue Radiation Damage After Pelvic Irradiation					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Improvement in symptoms	Shao et al 2011	8 /10	Direct	B	A complete response for improvement in symptoms was defined as all symptoms disappearing; a partial response was defined as the disappearance of clots but persistence of macroscopic haematuria. The proportion of patients showing a partial or complete response was high at the first follow-up point (6 months) for both the HBOT and HA groups but decreased over time. There was no significant difference between the groups at any of the follow-up points ($p>0.05$). For HBOT, 95% of patients showed a response at 6 months with most of these being a complete response. At 18 months this had reduced to 75% showing a response with approximately half showing a compete response. For HA, the response was 100% at 6 months with the majority complete responses, and 75% at 18 months with half complete responses. This was a small, single centre study. At baseline, patients had haemorrhagic cystitis of grade II (macroscopic haematuria) or grade III (macroscopic haematuria with the presence of clots and/or decrease in haemoglobin levels necessitating blood transfusions). At final follow-up after 18 months symptoms had disappeared in approximately half of the patients in both groups suggesting a similar effect for both treatments.

Change in voiding frequency	Shao et al 2011	8 /10	Direct	B	Frequency of voiding is the number of times that the patient urinates per day. Both groups showed a statistically significant improvement in voiding frequency at 6 months ($p<0.01$). For the HBOT group the number of voids per day decreased by a mean ± SD of 1.2 ± 1.1 from a baseline of 9.8 ± 1.7. For the HA group the number of voids per day decreased by 2.9 ± 1.7 from a baseline of 10.4 ± 1.8. No direct comparison between the groups was reported. For both HBOT and HA groups, voiding frequency reduced by 6 months but the improvement was not sustained over the 18 month follow-up period. In the HBOT group the improvement from baseline was no longer significant by 12 months follow-up with a mean decrease of 0.2 voids per day. In the HA group the improvement from baseline was still significant at 12 months follow-up with a mean decrease of 1.5 voids per day but was no longer significant by 18 months when the mean decrease in number of voids per day was 0.2. This was a small, single centre study. The improvement in number of voids per day was statistically significant but relatively small at 6 months follow-up and the improvement seen was not sustained over the follow-up period. By 12 months the mean improvement for the HBOT group was less than 1 void per day which is unlikely to be of clinical significance.
Change in pelvic pain	Shao et al 2011	8 /10	Direct	B	Pelvic pain was assessed using the visual analogue scale (VAS) ranging from 0 to 10. No descriptors for level of pain were provided but 0 typically represents no pain and 10 the worst possible pain on a VAS. The improvement in pain from baseline was statistically significant for both groups at all follow-up points ($p<0.05$). No direct comparison between the groups was reported. For the HBOT group the mean ± SD improvement at 6 months was 0.9 ± 0.8 from a baseline of 2.5 ± 2.2. The mean improved further at 18 months to 1.2 ± 1.2. For the HA group the greatest improvement was seen at 18 months with a mean (SD) improvement of 1.5 ± 1.2 from a baseline of 2.8 ± 2.2. This was a small, single-centre study. Pain scores improved significantly for both groups and this improvement was sustained over the follow-up period. However the size of the improvement was relatively small at between approximately 1 and 1.5 points on a 10-point scale and the mean baseline scores were at the lower end of the scale.
Safety	Shao et al 2011	8 /10	Direct	B	Incidence of urinary tract infection (UTI) was reported. The incidence of UTI was significantly higher in the HA group than the HBOT group at 6 months follow-up (43% vs. 10%) ($p=0.034$). The proportion of patients with UTI increased over the follow-up period for both groups. There was no significant difference between the groups at 12 or 18 months ($p=0.1$). At 18 months the incidence of UTI was 30% for the HBOT group and 50% for the HA group. The only side effect reported was UTI which was described as the main side effect of HA instillation. No side effects typically associated with HBOT were reported and the first follow-up point was 6 months after treatment completion.

					Therefore the extent of treatment-related complications is unclear. This was a small, single-centre study.

HA – Hyaluronic Acid Instillation; HBOT – Hyperbaric Oxygen Therapy; SD – Standard Deviation; UTI – Urinary Tract Infection; VAS – Visual Analogue Scale

Use of HBOT Vs. Argon Plasma Coagulation (APC) to Treat Soft Tissue Radiation Damage After Pelvic Irradiation					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Haemoglobin level	Álvaro-Villegas et al 2011	6 /10	Direct	C	Haemoglobin is a protein molecule in red blood cells that carries oxygen from the lungs to body tissues and returns carbon dioxide from body tissues back to the lungs. A normal haemoglobin level is between 13.8 and 17.2 g/dL for men and 12.1 to 15.1 g/dl for women. At final follow-up 3 months after treatment the mean ± SD haemoglobin level had improved from 10.3 ± 2.6 to 12.0 ± 2.1 for the HBOT group and had improved from 10.1 ± 2.1 to 11.3 ± 2.0 for the APC group. There were no significant differences between the HBOT and APC groups at any of the follow-up points. No significance tests were performed on the improvement from baseline. The gender of the patients was not reported. This was a small, non-randomised controlled study with patients who were receiving transfusions due to haemorrhage associated with rectal bleeding at baseline. The clinical significance of the improvement from baseline observed in both groups is not clear.
Number of transfusions	Álvaro-Villegas et al 2011	6 /10	Direct	C	Transfusion was required in these patients due to blood loss from rectal bleeding. The number of transfusions required decreased in both groups. A greater improvement was seen earlier in the APC group which had statistically significantly better results than the HBOT group at 1 and 2 months follow-up ($p<0.05$). At 1 month follow-up the number of transfusions required by the APC group had decreased from a mean ± SD of 4.8 ± 7.8 to 0.6 ± 1.1. This improvement was sustained at 2 and 3 months follow-up. In the HBOT group the number of transfusions required decreased at each month follow-up and at the final 3 month follow-up had decreased to 0.8 ± 1.2 from 3.8 ± 2.9 at baseline. No significance tests were performed on the improvement from baseline. This was a small, non-randomised controlled study with patients who were receiving transfusions due to haemorrhage associated with rectal bleeding at baseline. The time period over which the number of blood transfusions reported was received was not specified. A reduction is the number of blood transfusions required is likely to be of clinical benefit but the significance of the improvement seen is both groups is not clear.

Tissue toxicity	Álvaro-Villegas et al 2011	6 /10	Direct	C	Tissue toxicity was assessed by the LENT SOMA tissue toxicity score. No information on the scoring of this scale was provided in this study, however individual LENT SOMA items are generally scored on a scale of 1 to 4 and then summed, with higher scores suggesting more severe symptoms. Both groups showed an improvement in mean scores over the 3 month follow-up period. A greater improvement was seen in the APC group at 1 and 2 months ($p<0.05$) but there was no significant difference between the groups by 3 months. By 3 months the mean ± SD tissue toxicity for the HBOT group had improved from 12.2 ± 2.9 at baseline to 4.8 ± 3.5. For the APC group this improvement was from 13.3 ± 2.9 to 3.0 ± 3.5. Both HBOT and APC groups showed improvement in mean scores for tissue toxicity over 3 months, with greater improvements in the APC group at one and two months follow up. Without clear information on the scoring system used the clinical significance of the improvements observed is unclear. This was a small, non-randomised controlled study with patients who were receiving transfusions due to haemorrhage associated with rectal bleeding at baseline.
Safety	Álvaro-Villegas et al 2011	6 /10	Direct	C	Adverse events reported for the APC group included APC-associated rectal ulcers and rectal pain affecting 3 and 2 patients respectively (approximately 15-20%). Persistent rectal bleeding was in observed in 2 APC patients (21%) and 3 HBOT patients (18%). Two patients (from the HBOT group) had to undergo terminal colostomy for refractory bleeding; the other 3 patients switched treatments (e.g. from APC to HBOT or vice versa) and showed clinical improvement. No other adverse events were reported for HBOT. No significance tests were reported comparing number of adverse events for the 2 groups.

APC – Argon Plasma Coagulation; g/dL – grams per decilitre; HBOT – hyperbaric oxygen therapy; SD – standard deviation

9 Literature Search Terms

Search strategy *Indicate all terms used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients with a history of pelvic irradiation at least 6 months previously for malignant disease (T1-4, N0, M0)** who: a. are grade 2 or higher in any LENT SOMA category OR have grade 1 *** persistent or intermittent gastrointestinal or genitourinary symptoms attributable to previous radiotherapy AND b. whose symptoms are not relieved or rendered manageable by appropriate lifestyle advice, medication or other recognized intervention over a period of 3 months The following subgroups should also be considered: a. Those in whom there is no evidence of cancer recurrence b. Those who are treated in palliative circumstances, in the presence of tumour recurrence, for control of genitourinary and / or gastrointestinal symptoms c. Those who receive 30 or more hyperbaric oxygen treatments ** including disease of the rectum, prostate, testes, bladder, uterine cervix, uterine corpus, ovary, vagina, vulva with genitourinary, gastrointestinal or cutaneous symptoms *** or equivalent scores on another validated assessment tool
I – Intervention Which intervention, treatment or approach should be used?	20 or more hyperbaric treatments each delivering a maximum inspired partial pressure of oxygen between 200 and 253 kPa and lasting between 60 and 120 minutes (eg Royal Navy Table 66) administered 5 days each week
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Any / all other conservative medical management
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	<u>Critical to decision-making:</u> • Clinical effectiveness including: o Symptom severity o Presence and severity of haematuria o Maintenance of Hb within normal parameters o Need for transfusion o Bowel specific quality of life measures; o Bladder specific quality of life measures o Pain o Reversal of colostomy o Requirement for cystectomy

	o Requirement for proctectomy o Analgesic requirement; o Psychological morbidity o Quality of Life scores; o Activities of Daily Living; o Adverse Drug Reactions and other side-effects of treatment o Long term outcomes <u>Important to decision-making:</u> • Cost effectiveness

Assumptions / limits applied to search

Inclusion criteria

Peer reviewed studies published in the last 10 years including:
Systematic Reviews with / without meta-analyses
Case series
Cost effectiveness studies
Randomised Controlled Trials,
Well designed cohort studies

Exclusion criteria

Work that is not available in the English language
Grey literature including conference reports, abstracts, letters, posters
Unpublished studies
Case reports

10 Search Strategy

We searched PubMed, Embase, Cochrane Library, TRIP and NHS Evidence. Limiting the search to papers published in England from **1st January 2007 to 24th April 2017**. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 24th April 2017
Embase search:

1	exp radiation injury/	63140
2	exp radiotherapy/ae, co [Adverse Drug Reaction, Complication]	6646
3	exp urogenital tract tumor/rt [Radiotherapy]	49255
4	exp pelvis tumor/rt [Radiotherapy]	1073
5	exp large intestine cancer/rt [Radiotherapy]	5805
6	((radiation or radiotherap* or irradiat*) and (damag* or injur*)).ti.	9649
7	((radiation or radiotherap* or irradiat*) adj3 (damag* or injur*)).ti,ab.	20596
8	((pelvis or pelvic or gastro* or genitourin* or genito-urin* or genital or rectum or rectal or prostat* or testes or testic* or bladder* or cervical or cervix or uterus or uterine or ovary or ovaries or ovarian or vagina*) and (radiation or radiotherap* or irradiat*)).ti.	27123
9	((pelvis or pelvic or gastro* or genitourin* or genito-urin* or genital or rectum or rectal or prostat* or testes or testic* or bladder* or cervical or cervix or uterus or uterine or ovary or ovaries or ovarian or vagina*) adj3 (radiation or radiotherap* or irradiat*)).ti,ab.	25672
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	150788
11	hyperbaric oxygen/	15720
12	((hyperbaric adj2 (oxygen* or therap* or treatment)) or hbot or oxygen chamber* or	10992
13	11 or 12	17152
14	10 and 13	1009
15	(exp animals/ or nonhuman/) not human/	5931197
16	14 not 15	963
17	limit 16 to (english language and yr="2007 -Current")	474
18	conference*.pt.	3268924
19	17 not 18	377

11 Evidence Selection

- Total number of publications reviewed: 45
- Total number of publications considered potentially relevant: 16
- Total number of publications selected for inclusion in this briefing: 4

12 References

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Shao Y. Lu GL. Shen ZJ. 2011. Comparison of intavesical hyaluronic acid installation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. *BJU International* 109: 691-694.

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