CPAG Summary Report for Clinical Panel – URN 1778: Hyperbaric oxygen therapy (HBOT) for soft tissue radiation damage in patients with a history of pelvic irradiation for malignant disease

The Benefits of the Proposition – Hyperbaric oxygen therapy vs sham (placebo) treatment			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [A]	Neither of the 2 Randomised Control Trials (RCTs) comparing HBOT to sham (placebo) treatment reported any statistical analysis on differences in safety outcomes. Only one RCT (Glover et al 2016) reported safety outcomes by treatment group. Glover et al (2016) reported 8 serious adverse events (side effects) 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, which are changes affecting vision (including short sightedness (myopia)) and ear pain or barotrauma (injuries related to increased air or water pressure) 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 (tests to validate result) 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.
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review Hyperbaric oxygen therapy vs sham treatment			
No	Metric	Grade of evidence	Summary from evidence review
1.	Change in gastrointestinal symptoms	Grade 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) in 1 RCT (Glover et al 2016). 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.
2.	Change in rectal bleeding	Grade 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) in 1 RCT (Glover et al 2016). 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.
3.	Change in mean LENT SOMA score	Grade B	The LENT SOMA scale is an anatomic-specific morbidity scoring system for severity of radiation-induced complications. Symptoms are scored from grade 1 (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. Clarke et al (2008) 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 (results are

			unlikely due to chance) improvement in mean score from baseline was reported for both the HBOT (5.00) and sham groups (2.61) immediately after treatment in 1 RCT (Clarke et al 2008). 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. A direct comparison between the groups reported a significantly lower average score for HBOT than sham, 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.
4.	Improvement on clinical evaluation	Grade 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) in 1 RCT (Clarke et al 2008). 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.
5.	Change in bowel dysfunction (assessed using LENT SOMA)	Grade 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 in 1 RCT (Glover et al 2016). 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.
6.	Quality of Life	Grade 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. One RCT (Clarke et al 2008) 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.

The Benefits of the Proposition – Hyperbaric oxygen therapy vs intravesical hyaluronic acid instillation			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Benefit determined [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 in 1 RCT (Shao et al 2011). 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 hyperbaric air (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.
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [B]	Incidence of urinary tract infection (UTI) was reported in 1 RCT (Shao et al 2011). 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.
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review Hyperbaric oxygen therapy vs intravesical hyaluronic acid instillation			
No	Metric	Grade of evidence	Summary from evidence review
1.	Improvement in symptoms	Grade 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 in 1 RCT (Shao et al 2011). 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.
2.	Change in voiding frequency	Grade 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 ($p<0.01$) in 1 RCT (Shao et al 2011). 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.
3.		Choose an item.	
4.		Choose an item.	
5.		Choose an item.	

The Benefits of the Proposition – Hyperbaric oxygen therapy (HBOT) vs argon plasma coagulation (APC)			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events	Adverse events reported for the APC

		identified [C]	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. This (Álvaro-Villegas et al 2011) was a small, non-randomised controlled study with patients who were receiving transfusions due to haemorrhage associated with rectal bleeding at baseline.
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review Hyperbaric oxygen therapy (HBOT) vs argon plasma coagulation (APC)			
No	Metric	Grade of evidence	Summary from evidence review
1.	Haemoglobin level	Grade 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 (Álvaro-Villegas et al 2011) 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.
2.	Number of transfusions	Grade 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 (Álvaro-Villegas et al 2011)

			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.
3.	Tissue toxicity	Grade 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 (Álvaro-Villegas et al 2011)

			was a small, non-randomised controlled study with patients who were receiving transfusions due to haemorrhage associated with rectal bleeding at baseline.