Radiation-induced cystitis treated with hyperbaric oxygen therapy (RICH-ART): long-term follow-up of a randomised controlled, phase 2–3 trial

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Summary

Background Chronic radiation-induced cystitis is a common and often debilitating complication of radiotherapy for pelvic cancers, affecting approximately 5–10% of patients. Symptoms such as haematuria, urinary urgency, frequency, and dysuria significantly affect quality of life. Although hyperbaric oxygen (HBO2) alleviates symptoms, evidence regarding its long-term benefits is limited. This study reports on the 5-year follow-up of the RICH-ART trial, evaluating whether the therapeutic effects of HBO2 on chronic radiation-induced cystitis are sustained over a longer follow-up period.

Methods RICH-ART is a multicentre, open-label, phase 2–3 trial, conducted at five Nordic hospitals: Sahlgrenska and Karolinska (Sweden), Haukeland (Norway), Rigshospitalet (Denmark), and Turku (Finland). Eligible patients were aged 18–80 years, had completed pelvic radiotherapy at least 6 months earlier, had chronic radiation-induced cystitis, and an Expanded Prostate Cancer Index Composite (EPIC) urology score <80. Patients were randomised to receive HBO2 (30–40 sessions, 100% oxygen, breathed at 240–250 kPa, for 80–90 min daily) or standard of care with no restrictions for other medications or interventions (control group). No masking was applied. The primary outcome—change in EPIC urinary total score from baseline to 6 months— has been previously reported. After this point, patients in the control group were offered HBO2. Here, we report the secondary outcome: long-term symptom relief in all patients who received HBO2, measured as change in EPIC urinary total score from baseline to 5 years post-HBO2. Adverse events were recorded only during the period patients received HBO2. Follow-up was terminated 6 months early, in May 2022, due to administrative constraints, primarily lack of funding. RICH-ART is registered with ClinicalTrials.gov (NCT01659723), and with EudraCT (2012-001381-15).

Findings Of 223 patients screened between May 9, 2012, and Dec 20, 2017, 87 were enrolled and randomised. One patient in the intervention group and 7 patients in the control group withdrew consent immediately after randomisation. Of the remaining 79 patients, 74 completed the first part of the study. One patient in the control group declined HBO2 and three had missing data for the first year, making 70 patients eligible for follow-up. The mean EPIC urinary total score improved 18.0 points (95% CI 14.2–21.8) from 46.6 (SD 18.4) pre-HBO2 to 64.6 (SD 24.1) at 6 months, and the improvement remained stable at 19.1 points (95% CI 13.3–24.9) at year 5. Responders (n = 48; 68.6%), defined as those with ≥9-point improvement post-HBO2, maintained a mean increase of 22.9 (95% CI 16.2–29.6; p < 0.0001) at 5 years. Non-responders (n = 22; 31.4%) showed no early benefit (43.5 [SD 15.6] to 44.6 [SD 16.6]). Nine of the 70 patients (12.8%) received additional HBO2 for recurring symptoms.

Interpretation Our findings provide evidence for the long-term effects of HBO2 in the treatment of chronic radiation-induced cystitis. Sustained symptom relief over 5 years supports its potential as a key therapeutic option for managing chronic radiation-induced adverse effects. Further studies are needed to define optimal treatment protocols, identify predictive biomarkers, and evaluate health economic impact.

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Research in context

Evidence before this study

Prior to starting RICH-ART, we performed a health technology assessment of the use of hyperbaric oxygen therapy (HBO2) to treat radiation-induced adverse effects in the pelvic region. We searched PubMed from January 1, 1970, to April 5, 2011, using the terms "cystitis" AND "radiation" OR "radiation injuries" [Mesh] AND "hyperbaric" OR "hyperbaric oxygenation" [Mesh] OR "HBO" [tiab] OR "HBOT" [tiab], restricting the search to studies published in English, German, Danish, Norwegian, and Swedish. Only one non-randomized controlled study on radiation-induced cystitis was eligible for grading.

In 2023, a Cochrane review, including four randomized trials of radiation adverse effects in the pelvic region, concluded that while HBO2 may be associated with improved outcomes, more information is required about the time for which we can expect the benefits to persist.

Added value of this study

This study addresses a critical gap in the literature on the durability of the therapeutic effects of HBO2 on chronic radiation-induced cystitis. To our knowledge, this is the first study to report 5-year follow-up data of patients with chronic radiation-induced cystitis treated with HBO2. Our findings show that patient-reported improvements in urinary symptoms after HBO2 are sustained over 5 years, providing evidence of long-term benefits.

Implications of all the available evidence

Taken together with the findings of previous work, our results suggest that the integration of HBO2 into standard care may offer significant health and economic benefits. Further research is required to optimize dosing, assess cost-effectiveness, identify predictive biomarkers, and clarify the mechanisms underlying its benefits.

Introduction

Radiotherapy for cancer can cause both acute and delayed adverse effects.[1] Acute radiation-induced adverse effects manifest within weeks or months of exposure and often resolve spontaneously.[1,2] Adverse effects that develop or persist 6 months post radiotherapy are often referred to as late or chronic.[1–3] They usually remain stable or worsen over 4–10 years of follow-up.[4–7] Chronic radiation-induced cystitis affects 5–10% of patients treated for prostate, rectal, or gynaecological cancers.[3–6] It presents with symptoms such as pain, increased urinary frequency, urgency, incontinence, and dysuria, leading to significant impairment in quality of life, with some patients developing severe complications such as gross haematuria.[5,7–10] Since patient-reported outcome measures are not reported in most oncology registries, and chronic radiation-induced adverse effects are treated by general practitioners or urologists rather than oncologists, the problems may be underreported. While most patients experience mild symptoms and recover, a lower but not insignificant number have severe chronic radiation-induced cystitis, resulting in significantly worse urinary function.[4–7]

Chronic radiation-induced cystitis is driven by hypoxia, fibrosis, and vascular damage caused by radiation.[2,3] The pathogenesis begins with mucosal destruction, leading to ulcers, telangiectasia, and haematuria, as the bladder environment becomes hypovascular and hypocellular.[3,11] Vascular injury, including endothelial damage and disrupted angiogenesis, further exacerbates these effects, contributing to fibrosis and structural disorganisation of the bladder.[3,12] Additionally, neurogenic dysfunction likely plays a role in pain and impaired bladder control, highlighting the multifaceted nature of this condition.[12] The severity of chronic radiation-induced cystitis correlates with radiation dose, fraction size, and bladder volume exposed, with some cases resulting in life-threatening haemorrhage due to endarteritis obliterans and bladder wall fibrosis.[3]

Management of chronic radiation-induced cystitis is challenging, with treatments mainly limited to symptomatic relief, such as analgesics, intravesical coagulation and instillations.[3,7,9] In the RICH-ART trial, the largest prospective randomised trial on hyperbaric oxygen (HBO2) intervention for chronic radiation-induced cystitis, patients receiving HBO2 showed significant reductions in symptoms and improved quality of life at 6–8 months post-treatment compared to controls.[13] The HORTIS IV study reported similar effects of HBO2 on symptoms of radiation-induced proctitis when patients were assessed up to 5 years after treatment.[14] In contrast, the HOT2 study involving 84 patients found no significant benefit of HBO2 for radiation-induced

proctitis at a 1-year follow-up.[15] The latter study has been criticized for underdosing and having differences in patient selection and evaluation.[16] A positive effect of HBO2 on radiation induced adverse effects was further supported by a large Australian retrospective trial and a Cochrane review including 18 randomised trials.[17,18]

In addition to its clinical benefits, HBO2 has demonstrated significant cost advantages, with a recent study showing 37% lower health care costs in the intervention group than in the control group.[19] HBO2 also significantly reduced the need for endoscopic procedures because of haematuria, blood transfusions, and mortality by 31%, 78%, and 53%, respectively.[19]

Despite the documented beneficial effects of HBO2 as an intervention for chronic radiation-induced adverse effects, it is not yet widely integrated into clinical guidelines, or it is reserved as a last-line option for patients who have not responded to other interventions.[18,20–22] This presents a significant barrier to access for many patients despite evidence from both clinical trials and retrospective studies demonstrating that HBO2 may be effective in these conditions.[13,17,18,20–22] One objection to prescribing HBO2 for chronic radiation-induced adverse effects in the pelvic region has been the lack of evidence for long-term benefits.[18] Here, we present the 5-year follow-up analysis of the RICH-ART trial on HBO2 against chronic radiation-induced cystitis.

Methods

Study design

RICH-ART is a multicentre, randomised, controlled, open-label, phase 2–3 trial. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (ICH-GCP) guidelines. Ethical approval was obtained from the Regional Ethics Review Board in Gothenburg, Sweden (Dnr 025-10: 2010-02-25); the Swedish Medical Products Agency; and the corresponding authorities in the contributing countries. The trial was conducted and reported in accordance with the CONSORT 2010 statement. It was conducted at five Nordic university hospitals: Sahlgrenska in Gothenburg and Karolinska in Stockholm, Sweden; Haukeland in Bergen, Norway; Rigshospitalet in Copenhagen, Denmark; and Turku in Turku, Finland.

This report presents the 5-year follow-up of the RICH-ART trial, in which all participants—including those initially assigned to standard care—ultimately received HBO2. As such, the current analysis represents a single-group, longitudinal evaluation of long-term outcomes following intervention. All patients were fully informed about the design of the study and gave oral and written informed consent before any study-specific procedure.

Study participants

RICH-ART enrolled patients aged 18–80 years who had completed pelvic radiotherapy at least 6 months prior, had an Expanded Prostate Cancer Index Composite (EPIC) urology total score less than 80, and were diagnosed with chronic radiation-induced cystitis confirmed by a urologist as the likely cause of their symptoms.[13] Sex was recorded from clinical records as binary variable (male/female) based on medical classification. Exclusion criteria were bleeding requiring blood transfusion exceeding 500 mL within the past 4 weeks, incontinence requiring permanent catheter, bladder capacity less than 100 mL, fistula in the urinary bladder, previous treatment with HBO2 for late radiation-induced adverse effects, or contraindication to HBO2 (severe pulmonary or cardiac impairment; severe claustrophobia; pregnancy; not being oriented to person, time, or place; or unable to follow simple verbal commands).

Randomisation and masking

Patients were block randomised at a 1:1 ratio to receive either HBO2 or standard of care (control). No masking of patients or investigators was done. Allocation was computer-generated in blocks of four per stratification group. Randomisation was stratified by sex (male/female), time from radiotherapy to inclusion (≥12 versus <12 months), and previous invasive pelvic surgery—defined as pelvic surgery for malignant disease or any lower urinary tract surgery (yes/no).

Procedures

Patients in the intervention group received HBO2, i.e., breathing 100% oxygen at a pressure of 240–250 kPa in a hyperbaric chamber for 80–90 min 5 days per week for 6–8 weeks. Further details regarding the administration of HBO2 are described in the previous RICH-ART publication.[13] The effect of HBO2 was assessed 4–6 months after treatment. Patients in the control group were then also offered HBO2.[13] All those who received HBO2 were invited to participate in a predefined 5-year follow-up. The criteria for discontinuation of the study or follow-up included patient discretion, diagnosis of new cancer, incorrect enrolment, inability to answer EPIC, or administration of HBO2 for other conditions after enrolment. A new series of HBO2 sessions were allowed on a doctor's discretion basis to patients experiencing recurring symptoms of radiation-induced cystitis.

Participants were followed up at 6 and 12 months after HBO2 and then annually for a total of 5 years. Long-term outcomes were measured using the EPIC urinary domain, which consists of 12 items and measures various urinary tract symptoms such as leakage, incontinence, nocturia, pain, and haematuria.[23] Given the overlap between urinary and bowel symptoms,

patients were also asked to complete the EPIC bowel domain, which covers 14 items related to bowel function. Responses were recorded on a Likert scale and transformed into a score of 0–100, with lower values indicating more severe symptoms. Sub-scores were calculated for the function, bother, incontinence, and irritability/obstruction domains. EPIC has been validated not only for prostate cancer but also for female patients with pelvic radiation-induced adverse effects.[24]

We defined minimally clinically important difference to be an improvement of at least 9 points on the EPIC urinary score, which corresponds to approximately 0.5 SD, and are in line with previous validation of EPIC.[13,25] Participants whose EPIC score improved 9 or more points from baseline to 6 months after HBO2 were defined as responders to HBO2 and all other participants as non-responders.

Outcomes

The primary outcome for RICH-ART was change in patient-perceived urinary symptoms from before HBO2 to 6 months after HBO2, assessed with the EPIC urinary score.[13] Here, we report the prespecified secondary outcome: change in EPIC urinary total score from baseline to 5 years post-HBO2. We also report yearly development of EPIC bowel total score for all patients and EPIC urology total score for all patients, responders, and non-responders, respectively. Adverse events were registered only during the period patients received HBO2.

Statistical analysis

All statistical analyses were conducted by the research group in collaboration with professional experts in medical statistics, using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), as prespecified in the statistical analysis plan (SAP).

The target sample size was calculated for the primary outcome to detect an absolute change of 15 points in the EPIC urinary total score, given an SD of 23. To exceed 80% power using a two-tailed t-test at 0•05 significance level, 37 patients were needed in each study group, which was rounded up to 40 patients per group.[13]

For this long-term follow-up, changes in EPIC scores were analysed using a linear mixed model for repeated measures, with time (visit) included as a fixed effect. When analysing responder groups, responder status and its interaction with time were included as fixed effects. An autoregressive correlation structure of order 1 (AR(1)) was applied to model within-subject correlation over time, assuming stronger correlation between adjacent time points.

Baseline values (pre-HBO2) were compared with those at 6 months and at each annual follow-up (1–5 years) with within-group differences estimated using least squares means from the model. The normality of within-subject differences was assessed using visual inspection of histogram and Q–Q plots and was considered acceptable for all time points. Homogeneity of variance was also confirmed.

Missing data from year 5 were handled using several approaches: complete case analysis, last observation carried forward, and stochastic regression imputation, as predefined in the SAP. Stochastic regression imputation was performed using fully conditional specification regression imputation model, with the 5-year EPIC urinary total score as the dependent variable and prior time points, age, weight, height, external radiation energy, type of cancer, and presence of urethral stricture as predictors. In addition, a post-hoc multiple regression imputation was performed to further assess the robustness of the findings, generating 50 imputed datasets (M = 50). For within-group comparisons, Fisher's non-parametric permutation test for matched pairs was used.

Between-group comparisons (responders versus non-responders) were exploratory, and no formal testing of group differences was conducted.

All statistical tests were two-tailed with a significance level set at 0.05. Descriptive statistics including means, SD, medians, and 95% CI, for all EPIC scores. Long-term longitudinal trends were graphically depicted using line plots.

The study is monitored by an independent institution (Gothia Forum, Gothenburg, Sweden) and is registered with the European Medicines Agency (EudraCT 2012-001381-15) and ClinicalTrials.gov (NCT01659723). The protocol and SAP are available in the Supplement.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study. NO had final responsibility for the decision to submit the manuscript for publication.

Results

Between May 9, 2012, and Dec 20, 2017, 87 (39%) patients of 223 screened, were randomised to the RICH-ART trial. Of the 87 included patients, 74 (85.1%) completed the first part of the study. The follow-up was terminated in May 2022, 6 months prematurely due to administrative reasons, primarily lack of funding. All but one patient in the control group underwent HBO2 after the intervention.

During the first year of follow-up, three patients were lost: two withdrew consent and one underwent urinary diversion *ad modum Bricker*. Therefore, the follow-up cohort consisted of 70 patients who provided follow-up data at least once during the 5-year period (Table 1). A

Patient characteristics	All (n = 70)
Age (years)	63.8 (12.7)
BMI (kg/m^2)	28.6 (6.0)
Sex	
Male	48 (68.6%)
Female	22 (31.4%)
Nicotine use	
No	59 (84.3%)
Yes	11 (15.7%)
Cancer type	
Prostate	46 (65.7%)
Cervix	18 (25.7%)
Rectum	3 (4.3%)
Uterus	2 (2.9%)
Rectum	1 (1.4%)
Haematuria score	
Nil	35 (50.0%)
Trace	3 (4.3%)
+	6 (8.6%)
++	12 (17.1%)
+++	14 (20.0%)

Data are n (%) or mean (SD). BMI = Body Mass Index.

Table 1: **Patient characteristics.**

CONSORT flow diagram is provided to illustrate participant enrolment, allocation, follow-up, and analysis (Fig. 1).

The mean EPIC urinary total score increased 18.0 points (95% CI 14.2–21.8) from before HBO2 (mean 46.6, SD 18.4) to 6 months post-HBO2 (mean 64.6, SD 24.1), and remained stable until 5 years (mean 65.7, SD 22.7) (Table 2). The mean increase in EPIC urinary total score from before HBO2 to 5-year follow-up was 19.1 (95% CI 13.3–24.9; $p < 0.0001$) (Table 3, Fig. 2). Sensitivity analyses, including both the last observations carried forward, multiple and stochastic regression imputation methods, supported these results (all $p < 0.0001$) (Table 3). EPIC urology sub-scores at 6 months post-HBO2 are included in the Supplement. The proportions of missing data, from the 70 included patients, were 2 (2.9%) at year 1, and 5 (7.1%), 11 (15.7%), 15 (21.4%) and 31 (44.3%) for year 2–5, respectively.

Six months after HBO2, the patients were classified as responders or non-responders based on the improvement in the mean EPIC urinary total scores before HBO2. Of the 70 patients, 48 (68.6%) were responders and showed improvement from before HBO2 (mean 48.0 [SD 19.5]) to 6 months after HBO2 (mean 73.7 [SD 21.4]; change 25.7 [95% CI 21.5–30.0]). This improvement remained stable over time, with a mean increase of 22.9 (95% CI 16.2–29.6; $p < 0.0001$) at 5 years. Non-responders (n = 22; 31.4%) did not change their mean EPIC urinary total score from before HBO2 to 6 months after HBO2; (43.5 [SD15.5] to 44.6 [SD16.6]). This group showed a wide span in 95% CI for change in EPIC at year 1 (3.3–18.7) and year 5 (1.5–23.0) (Table 2).

The mean EPIC bowel total score for all patients, which also increased 6 months after HBO2, remained stable throughout the follow-up period, demonstrating sustained symptom relief across both the urinary and bowel domains (Table 4).

Adverse events related to HBO2 were reported in the initial RICH-ART publication: pain from equalising difficulties in 6 of 41 events, (15%), hyperoxia-induced transient myopia in 5 events (12%), and barotrauma in 4 events (10%).[13]

The wide span in 95% CI among the non-responders prompted a post hoc analysis of this group showing that 5 patients of 22 (22.7%) had a delayed response to HBO2 with an increase in mean EPIC urinary total score of 36.97 (95% CI 19.66–54.28) at year 1 that was sustained during the follow-up period, with increase in mean EPIC urinary total score of 33.08 (95% CI 14.73–51.44) at their last recorded visit (not shown). The remaining patients in the non-responder group had either no change or a decline in their EPIC urology total score during the follow-up (not shown).

Nine of the 70 (12.8%) patients experienced recurring symptoms of radiation-induced cystitis one year or more after the initial session of HBO2 and underwent 20-30 additional sessions of HBO2.

Discussion

This 5-year follow-up of the RICH-ART trial demonstrated that the improvement in patient-reported symptoms of chronic radiation-induced cystitis observed after 30–40 HBO2 sessions persists over time. These findings are in line with a long-term study by Pereira et al., which focused on haematuria and demonstrated the sustained benefits of HBO2 in its management.[26] Similarly, Nakada et al. demonstrated significant long-term improvements in radiation cystitis symptoms among patients with prostate cancer, with efficacy ratios remaining stable beyond 7 years and 74% of patients achieving favourable outcomes.[27] Notably, both studies emphasized that earlier initiation of HBO2 following symptom onset is associated with better outcomes, highlighting the importance of timely intervention. By contrast, the RICH-ART trial assessed a broader range of symptoms associated with radiation cystitis, thereby providing a more comprehensive evaluation of the impact of HBO2. Our results are also in line with the findings of the HORTIS IV trial, which reported sustained improvements in quality of life and symptom alleviation in patients with radiation-induced proctitis.[14] At the completion of the HORTIS IV study 14 of 120 patients (12%) of the randomised patients had completed follow-up assessment for year 5. In contrast, our study, in which 39 of 70 patients (56%) were eligible for assessment 5 years after HBO2, provided a more robust follow-up.

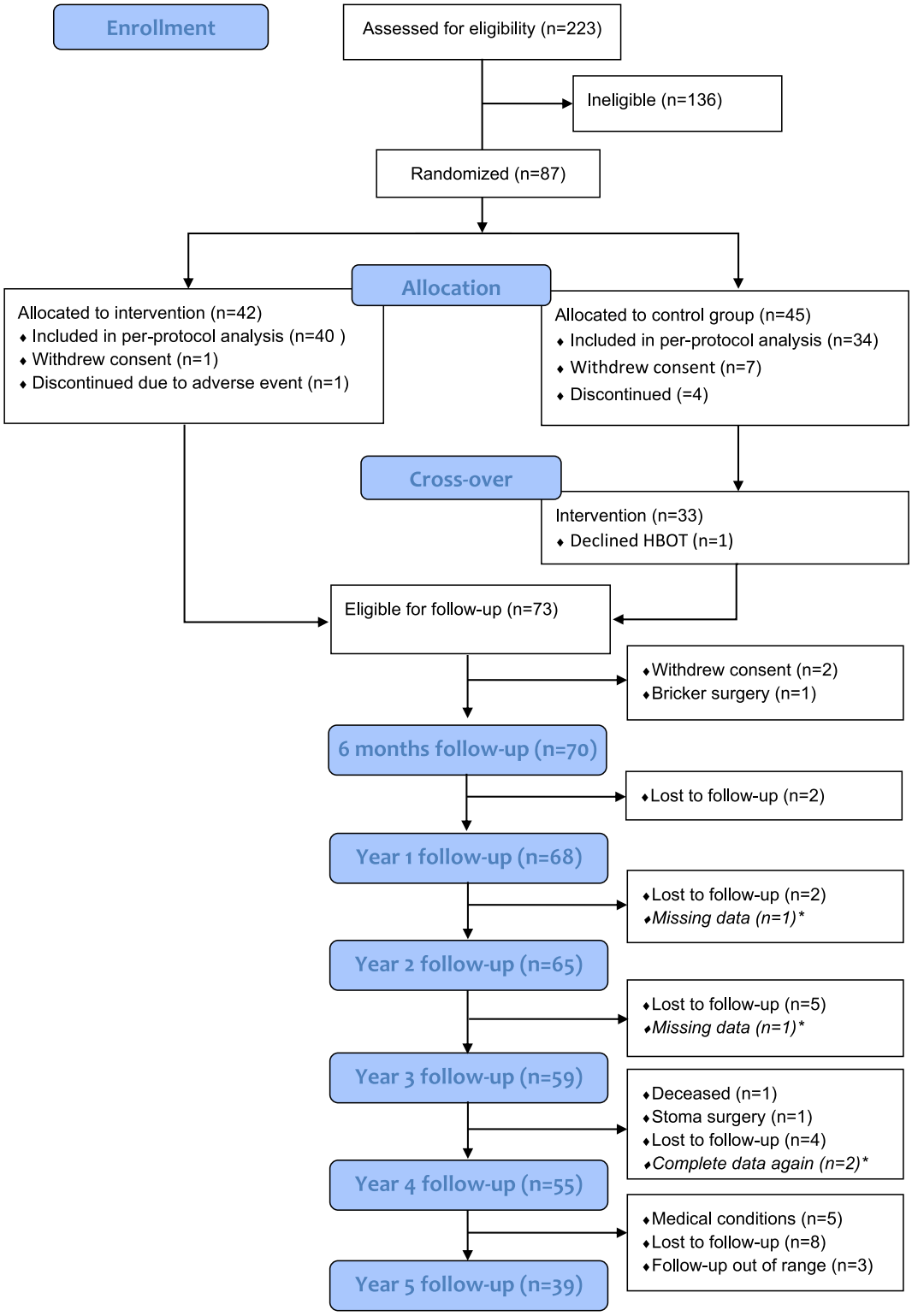

Fig. 1: **Consort Flow-diagram.** *One individual had missing data year two and three and one subject had missing data year three. Both had complete data for years four and five.

Visit	Variable	Total	Responder	Non-responder
Baseline	EPIC urinary total score	46.6 (18.4), n = 70	48.0 (19.5), n = 48	43.5 (15.6), n = 22
6 months post HBO2	EPIC urinary total score	64.6 (24.1), n = 70	73.7 (21.4), n = 48	44.6 (16.6), n = 22
	Change in EPIC urinary total score from baseline	18.0 (14.2–21.8), p < 0.0001	25.7 (21.5–30.0), p < 0.0001	1.1 (−5.1 to 7.4), p 0.72
Year 1 post HBO2	EPIC urinary total score	66.1 (21.3), n = 68	71.5 (18.6), n = 47	54.4 (22.5), n = 21
	Change in EPIC urinary total score from baseline	19.5 (15.0–24.0), p < 0.0001	23.5 (18.2–28.7), p < 0.0001	11.0 (3.3–18.7), p 0.005
Year 2 post HBO2	EPIC urinary total score	66.5 (20.8), n = 65	71.2 (20.1), n = 46	56.5 (18.9), n = 19
	Change in EPIC urinary total score from baseline	19.9 (15.1–24.8), p < 0.0001	23.2 (17.6–28.8), p < 0.0001	12.6 (4.5–21.5), p 0.003
Year 3 post HBO2	EPIC urinary total score	65.6 (22.2), n = 59	71.4 (19.8), n = 40	53.4 (22.7), n = 19
	Change in EPIC urinary total score from baseline	19.0 (13.9–24.1), p < 0.0001	23.4 (17.4–29.4), p < 0.0001	9.9 (1.1–18.7), p 0.027
Year 4 post HBO2	EPIC urinary total score	63.9 (21.9), n = 55	72.4 (17.5), n = 36	46.8 (20.1), n = 19
	Change in EPIC urinary total score from baseline	17.3 (12.1–22.5), p < 0.0001	24.4 (18.2–30.7), p < 0.0001	3.3 (−5.6 to 12.3), p 0.46
Year 5 post HBO2	EPIC urinary total score	65.7 (22.7), n = 39	70.9 (19.5), n = 29	55.7 (26.6), n = 10
	Change in EPIC urinary total score from baseline	19.1 (13.3–24.9), p < 0.0001	22.9 (16.2–29.6), p < 0.0001	12.2 (1.5–23.0), p 0.025

Level at each visit is presented as mean (SD) and n. Change is presented as mean with 95% CI and p-value.

Table 2: **EPIC urinary total score for all patients, responders, and non-responders.**

We report sustained symptom relief after HBO2 for chronic radiation-induced proctitis and cystitis. Although such symptoms may vary over time, once the condition has become chronic, it rarely recovers spontaneously, especially when ischaemia and fibrosis have set in, making it implausible that our results were caused by spontaneous improvements in the EPIC score.[3] A mean improvement of 19.1 points on the EPIC urinary total score, with a 95% CI of 13.3–24.9, after 5 years exceeds the validated threshold for minimally clinically important difference of 9–10 points, as proposed in previous validation studies, supporting the clinical relevance of the effect.[25]

Patients with less than a nine-point improvement on EPIC at 6 months after HBO2 were classified as non-responders. However, 5 of these patients showed sustained EPIC urinary score improvements exceeding 9 points at 1 and 5 years, making them late responders rather than non-responders. This indicates that 6 months may be too early to fully assess the benefits of HBO2 and makes the argument for the benefits of HBO2 even stronger than in the initial 6 months analysis.

Nine patients received 20–30 sessions of additional HBO2 during the follow-up period due to recurring radiation-induced symptoms. Seven of these were from one centre where each HBO2 series comprised 30 sessions, versus 40 in the other centres. As there were no common criteria for re-treatment, it is unclear if the relapsing rate is higher after 30 compared to 40 treatments, or if these numbers reflect other differences in the patient management between centres.

In a study assessing health-related quality of life amongst 1014 patients treated for prostate cancer, EPIC urinary scores for different domains among patients that were not radiated were around 90 (88.2–92.9). One year after external radiation therapy, EPIC scores had declined significantly (EPIC Urinary irritative 83.2 [99% CI 80.5–85.9] and EPIC bowel 85.4 [99% CI 83.1–87.8]).[23] In the RICH-ART trial, one of the inclusion criteria was EPIC urinary total score under 80. But the mean EPIC urinary total score before HBO2 was much lower at 46.6 (SD 18.4). Hence, all patients included in the RICH-ART trial had more severe symptoms of chronic radiation-induced cystitis, such as daily pain, leakage, and/or bleeding, and symptom relief may have a significant impact on the health-related quality of life.[13]

Whether HBO2 would have the same benefit as observed in this study in a cohort of patients with less severe chronic radiation-induced adverse effects remains to be investigated.

The study was not blinded and lacked a long-term control group, which are two major limitations. HBO2 has already been integrated into the standard protocol for the treatment of chronic radiation-induced adverse effects at participating centres, despite the lack of robust scientific evidence. Hence, we were unlikely to recruit enough patients willing to withhold HBO2 for at least 5

EPIC urinary total score	n	EPIC urinary total score	Mean change in EPIC urinary total score	p value within group
Pre-HBO2	70	46.6 (18.4)		
5 years	39	67.7 (22.7)	18.5 (11.2–25.9)	<0.0001
5 years, linear mixed model for repeated measures	–	65.7 (22.7)	19.1 (13.3–24.9)	<0.0001
5 years, Last visit carried forward	70	64.8 (22.6)	18.2 (13.2–23.2)	<0.0001
5 years, Stochastic imputation	70	63.3 (23.9)	16.8 (10.8–22.7)	<0.0001
5 years, Multiple imputation	70	62.6 (SEM 3.33)	16.0 (9.1–22.9)	<0.0001

Level values are presented as mean (SD) and changes as mean with 95% CI. For comparison within groups the Fisher's non-parametric permutation test for matched pairs was used. SEM = standard error of the mean.

Table 3: **Change in EPIC urinary total score - Sensitivity analysis.**

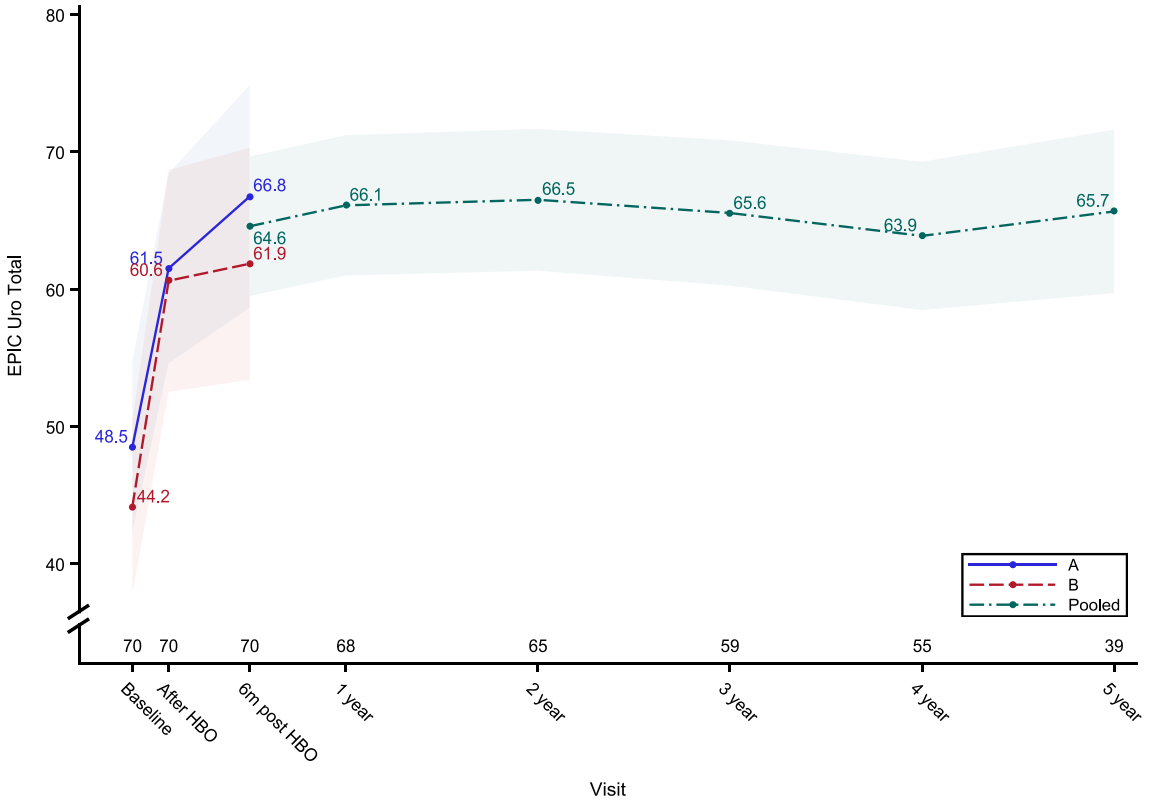

Fig. 2: **EPIC urinary total score from baseline to year 5.** Mean EPIC urinary total score (EPIC Uro Total) with standard deviation, where the blue line and shadow represent the intervention group (A), the red line and shadow represent the control group (B), and the green line and shadow represent all patients that received HBO2 (Pooled).

years. We determined that the longest period for which we could pragmatically withhold HBO2 was 6 months. The study design allowed us to balance patient care with the study objectives, while offering delayed treatment to control participants after the initial 6 months. The lack of a control group resulted in a pre-post design that limited the ability to attribute observed improvements to HBO2. Furthermore, the longitudinal follow-up with repeated measures over years, without a control group, is susceptible to regression to the mean and time-trends independent of received treatment.

Another limitation of the study is the incomplete follow-up data, primarily due to the early termination of the trial before all patients reached the 5-year endpoint. This resulted in missing data for 16 patients at the 5-year follow-up. This issue stemmed from administrative challenges, affecting all centres and participants equally, thus minimising potential bias. We were unable to obtain complete medical data for all patients with missing data which constitutes a potential bias. However, sensitivity analyses indicated that the cohort assessed at 5 years remained representative of the initial study population, reinforcing the reliability of the long-term results. Although sensitivity analyses supported a sustained effect of HBO2, the proportion of missing data and the relatively wide 95% CIs limits the precision of the long-term estimates.

This study has several strengths, including its prospective design, comparably long follow-up time, and the fact that it was part of a multicentre, randomised controlled trial conducted in compliance with ICH-GCP standards, ensuring the integrity and quality of the

Variable	Baseline	6 months	1 year	2 years	3 years	4 years	5 years
EPIC Bowel total score	60.5 (22.2), n = 69	72.8 (17.6), n = 69	73.3 (19.1), n = 67	72.3 (19.1), n = 64	73.6 (20.4), n = 57	72.0 (19.6), n = 54	68.8 (22.8), n = 39

Data are mean (SD) and number of measures with mean estimated from repeated measure analysis.

Table 4: **EPIC Bowel total score.**

collected data. To our knowledge, this is the largest prospective cohort study on radiation-induced cystitis to date.

HBO2 shows promise for managing chronic radiation-induced cystitis by providing long-term symptom relief. The variability in responses among patients underscores the importance of identifying predictors of response to guide treatment decisions. A deeper exploration of the biological and clinical factors influencing treatment response could help tailor interventions more precisely, select patients, and optimise outcomes. A higher number of patients requiring repeated HBO2 amongst those that initially received 30 versus 40 HBO2 sessions highlights the need for dose-response trials. Future clinical trials that focus on the timing and sequencing of HBO2, including preconditioning or early intervention after radiotherapy, to maximise therapeutic outcomes are also needed.

Contributors

All authors contributed significantly to the development and completion of this study. NO and HS-L made substantial contributions to the conception and design of the study. NO led the establishment of the major collaborating sites and acted as coordinator of the study. NO, BM, AK, and LR-K were responsible for data collection. NO and HS-L had full access and verified the data. Statistical analysis was conducted by Statistiska Konsultgruppen, Gothenburg Sweden with input from NO, AR, and HS-L. The manuscript was drafted by NO and critically reviewed by all authors. NO was responsible for the final decision to submit the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work, ensuring that any issues related to accuracy or integrity are investigated and resolved.

Data sharing statement

The data supporting the findings of this study will be made available upon reasonable request. De-identified participant data, the study protocol, statistical analysis plan, and informed consent forms will be available beginning six months after publication of the article. Data will be shared with researchers who provide a methodologically sound proposal and who agree to use the data only for research purposes. Requests for data should be made to corresponding author's email. The data will be available for a period of three years following the article's publication.

Declaration of interests

OE has received national academic research grant from hospital district of southwest Finland. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103214.

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