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

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Summary

Background Late radiation cystitis is an adverse effect of cancer treatment with radiotherapy in the pelvic region. Symptoms of late radiation cystitis can be assessed with the Expanded Prostate Index Composite Score (EPIC). Previous reports indicate that hyperbaric oxygen therapy reduces symptoms from late radiation cystitis, but the evidence is predominantly based on non-randomised and retrospective studies. We aimed to assess whether hyperbaric oxygen therapy would mitigate symptoms of late radiation cystitis.

Methods We did a randomised, controlled, phase 2–3 trial (RICH-ART [Radiation Induced Cystitis treated with Hyperbaric oxygen—A Randomised controlled Trial]) at five Nordic university hospitals. All patients aged 18–80 years, with pelvic radiotherapy completed at least 6 months previously, a score of less than 80 in the urinary domain of the Expanded Prostate Index Composite Score (EPIC), and referred to participating hyperbaric clinics due to symptoms of late radiation cystitis, were eligible for inclusion. Exclusion criteria were ongoing bleeding requiring blood transfusion exceeding 500 mL in the past 4 weeks, permanent urinary catheter, bladder capacity less than 100 mL, fistula in the urinary bladder, previous treatment with hyperbaric oxygen therapy for late radiation injuries, and contraindications to hyperbaric oxygen therapy. After computer-generated 1:1 randomisation with block sizes of four for each stratification group (sex, time from radiotherapy to inclusion, and previous invasive surgery in the pelvic area), patients received hyperbaric oxygen therapy (30–40 sessions, 100% oxygen, breathed at a pressure of 240–250 kPa, for 80–90 min daily) or standard care with no restrictions for other medications or interventions. No masking was applied. The primary outcome was change in patient-perceived urinary symptoms assessed with EPIC from inclusion to follow-up at visit 4 (6–8 months later), measured as absolute change in EPIC urinary total score. RICH-ART closed enrolment on Dec 31, 2017; the last follow-up data will be compiled in 2023. RICH-ART is registered with ClinicalTrials.gov, number NCT01659723, and with the European Medicines Agency, number EudraCT 2012-001381-15.

Findings Of 223 patients screened between May 9, 2012, and Dec 20, 2017, 87 patients were enrolled and randomly assigned to either hyperbaric oxygen therapy (n=42) or standard care (n=45). After excluding eight patients who withdrew consent directly after randomisation (one in the hyperbaric oxygen therapy group and seven in the standard care group), 79 were included in the intention-to-treat analyses (n=41 in the hyperbaric oxygen therapy group, n=38 in the standard care group). Median time from randomisation to visit 4 was 234 days (IQR 210–262) in the hyperbaric oxygen therapy group and 217 days (195–237) in the standard care group. The difference between change in group mean of EPIC urinary total score at visit 4 was 10·1 points (95% CI 2·2–18·1; p=0·013; 17·8 points [SD 18·4] in the hyperbaric oxygen therapy group *vs* 7·7 points [15·5] in the standard care group). 17 (41%) of 41 patients in the hyperbaric oxygen therapy group experienced transient grade 1–2 adverse events, related to sight and hearing, during the period of hyperbaric oxygen therapy.

Interpretation Our results suggest that hyperbaric oxygen therapy relieves symptoms of late radiation cystitis. We conclude that hyperbaric oxygen therapy is a safe and well tolerated treatment.

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Introduction

Radiotherapy for cancer has both acute and late side-effects. Acute radiation injuries usually occur within weeks or a few months after exposure, whereas late tissue injuries occur or persist months to several years after radiotherapy.[1,2] Late radiation cystitis is a chronic and progressive condition that is reported in 5–15% of patients after radiotherapy to the pelvic area (eg, for prostate, rectal, or gynaecological cancers).[3] Symptoms include haematuria, increased urinary frequency and urgency, incontinence, and dysuria, which diminish the affected individuals' quality of life, often with further deterioration over time.[4] The pathophysiology of late radiation cystitis is not completely understood.[5] Previous work[1,2,5] has

Research in context

Evidence before this study

Before the initiation of our study, we did a health technology assessment, focusing on the use of hyperbaric oxygen therapy and late radiation injuries in the pelvic region. We searched PubMed from Jan 1, 1970, to April 5, 2011, for "cystitis" AND "radiation" OR "radiation injuries" [Mesh] AND "hyperbaric" OR "hyperbaric oxygenation" [Mesh] OR "HBO" [tiab] OR "HBOT" [tiab], limiting our results to the English, German, Danish, Norwegian, and Swedish languages. We found one non-randomised, controlled study focusing on late radiation cystitis, which qualified for grading. Although there were several other studies, these had serious limitations, such as being retrospective, uncontrolled, and small. A few prospective, non-randomised studies have been published since our search, reporting on reduction of haemorrhage and other symptoms in late radiation cystitis after hyperbaric oxygen therapy. Although there are a few randomised controlled and even blinded studies assessing other pelvic organs, a Cochrane report published in 2016 concluded that high-grade evidence is still scarce, especially for late radiation cystitis, and that more research is needed.

Added value of this study

RICH-ART is a randomised, controlled, multicentre study with the aim to test the addition of hyperbaric oxygen therapy to current standard care. This report supports the previous positive results of hyperbaric oxygen therapy in late radiation cystitis, focusing not only on patient-perceived urological symptoms, but also assessing bowel function, health-related quality of life, and macroscopic appearance of the bladder. It adds further support for hyperbaric oxygen therapy as treatment for a broad range of symptoms frequently experienced by patients with late radiation cystitis. It also suggests that hyperbaric oxygen therapy reverses macroscopic changes in the urinary bladder induced by radiotherapy.

Implications of all the available evidence

Many long-term cancer survivors have debilitating symptoms after radiotherapy to the pelvic region, with impaired health-related quality of life, and receive little benefit from available standard care. Considering previous reports in this field, and the added value of RICH-ART, we conclude that there is considerable support for adding hyperbaric oxygen therapy to the standard of care for patients with late radiation cystitis in the pelvic region.

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shown reduced vascular and cellular density in both urothelial and smooth muscular layers of the bladder after radiotherapy. Chronic inflammation and fibrosis are characteristics of late radiation cystitis, impairing the complex neuromuscular interplay responsible for proper storage and release of urine.[1,2,5]

Treatment of late radiation cystitis is challenging.[5] Mild and moderate cases are usually treated with a combination of anticholinergic drugs and training of pelvic floor muscles (often with poor response), and sometimes with the addition of analgesics and incontinence pads.[6] In serious cases, with debilitating symptoms and severe haematuria, hospital care is frequently required, including blood transfusions and bladder irrigation to prevent urinary retention caused by blood clots. Interventions such as blood clot evacuation or coagulation of bleeding bladder vessels, using general or regional anaesthesia, are often necessary. Instillation of locally acting agents such as hyaluronic acid, alum, or formaldehyde solution are frequently tried in cases with diffuse recurrent bleeding. However, although these treatments can be helpful in the short term, recurrence and re-treatment rates are very high, and late side-effects can be serious including necrosis, fistulation, and fibrosis of the bladder. Cystectomy and urinary diversion are necessary in the most severe and persistent cases.[6,7]

In some countries, hyperbaric oxygen therapy is part of treatment algorithms for haemorrhagic cystitis and is a treatment option to alleviate symptoms of late radiation cystitis.[7] It is also used for late radiation tissue injury in other organs such as the bowel and rectum, genital organs, and in the head and neck area.[3,7] Patients undergoing hyperbaric oxygen therapy breathe pure oxygen at an increased ambient pressure in a hyperbaric chamber designed for either one (monoplace) or several (multiplace) patients. During hyperbaric oxygen therapy, the serum partial pressure of oxygen and tissue oxygenation increase, creating a steep oxygen gradient from healthy to hypoxic tissue in the radiated area. Repeated therapy has been shown to stimulate stem cell mobilisation, increase neoangiogenesis, and reduce inflammation.[8] Several retrospective reports and three prospective non-randomised studies have shown that hyperbaric oxygen therapy alleviates symptoms of late radiation cystitis.[3,9–11] In the only published randomised controlled trial to date, the effects of hyperbaric oxygen therapy were compared with instillation of hyaluronic acid in patients with haemorrhagic radiation cystitis. Objective findings of both haematuria and pain decreased in both groups.[12] Another randomised controlled trial (NCT00134628) aimed to assess urinary symptoms after radiotherapy but was prematurely stopped due to low recruitment.

When assessing the scientific evidence for hyperbaric oxygen therapy in late radiation cystitis, we found it to be weak,[13] and therefore aimed to expand evidence on the effect of hyperbaric oxygen therapy on symptoms of late radiation cystitis by doing a randomised, controlled trial. Our hypothesis was that hyperbaric oxygen therapy would relieve the symptoms of late radiation cystitis and

reduce or reverse damage to urinary bladder function and structure.

Methods

Study design and participants

RICH-ART (Radiation Induced Cystitis treated with Hyperbaric oxygen—A Randomised controlled Trial) is an investigator-initiated, multicentre, randomised, unblinded, controlled, phase 2–3 trial done at five Nordic university hospitals (Gothenburg and Stockholm in Sweden, Bergen in Norway, Copenhagen in Denmark, and Turku in Finland; appendix).

See Online for appendix

Patients referred to a participating centre for treatment of late radiation cystitis were consecutively assessed by a hyperbaric physician for the following eligibility criteria: men or women aged 18–80 years, intended curative radiotherapy (primary or adjunctive) of the pelvic region completed at least 6 months ago, late radiation cystitis considered the most probable cause of symptoms (assessed by an urologist), and a value of less than 80 points in the urinary domain of the Expanded Prostate Index Composite Score (EPIC).[14] 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 hyperbaric oxygen therapy for late radiation injuries, or contraindication to hyperbaric oxygen therapy (severe pulmonary or cardiac impairment; severe claustrophobia; pregnancy; not being oriented to person, time, or place; or unable to follow simple verbal commands). Although smoking was strongly discouraged at all centres, two centres accepted patients who smoked. Potentially eligible patients were invited to screening (visit 1), which included cystoscopy and baseline assessment (demographic data, medical history, physical examination, laboratory assessment, EPIC, and health-related quality of life questionnaire).

The study was approved by the responsible institutions for medical research ethics for all participating centres and done in compliance with The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice, national laws, applicable regulatory requirements, and the ethical principles of the Declaration of Helsinki. The study was approved by the Regional Ethics Review Board in Gothenburg, Sweden (Dnr 025-10: 2010-02-25) and by the National Medical Product Agency of Sweden. All patients were fully informed about the design of the study and gave oral and written informed consent before any study-specific procedure.

Randomisation and masking

After completion of visit 1, eligible patients were randomly assigned in a 1:1 ratio to receive either hyperbaric oxygen therapy or standard care. No attempt was made to mask patients or investigators to the allocated intervention. The allocation was computer generated with block sizes of four for each stratification group. The investigators had no possibility to influence the randomisation, nor to change the allocated group. Randomisation was stratified by sex (male *vs* female), time from radiotherapy to inclusion (≥12 months *vs* <12 months), and previous invasive surgery in the pelvic area, defined as either pelvic surgery for malignant disease or surgery to the lower urinary tract for any reason (yes *vs* no).

Procedures

Patients in the intervention group received hyperbaric oxygen therapy (100% oxygen breathed at a pressure of 240–250 kPa for 80–90 min) five times per week (treatment period defined as visit 2). Starting within 4 weeks from visit 1, between 30 and 40 treatment sessions (within 60–80 days, counting from the first treatment) were given in a multiplace or monoplace chamber according to standard procedures at the respective hyperbaric centre. Visit 3 included a safety assessment and was done directly after the end of hyperbaric oxygen therapy (at around 2 months after randomisation). The standard care group did not receive any study-specific treatment, and no study-specific changes were made to ordinary prescribed medications in either group. Both the hyperbaric oxygen therapy group and the standard care group repeated all examinations 6–8 months after randomisation (visit 4). After completion of visit 4, all patients in the standard care group were offered hyperbaric oxygen therapy (figure 1). Criteria for discontinuation of the study, including follow-up, were: patient discretion, new cancer, incorrect enrolment, clinically significant complications related to hyperbaric oxygen therapy, and hyperbaric oxygen therapy for other conditions given after enrolment.

Symptoms of late radiation cystitis were assessed with the urinary domain of EPIC, a patient-reported outcome questionnaire giving an overall rating for the past 4 weeks. EPIC consists of 12 items regarding a broad range of patient-perceived urinary tract symptoms (leakage, frequency, incontinence, nocturia, pain, and haematuria). Answers are given on Likert scales that are transformed to a 0–100 score, in which a lower value indicates more severe symptoms. In addition to a total score, which is the mean of all included scores, the results can also be used to compile four domain subscores (function, bother, incontinence, and irritable/obstructive).[14] Several EPIC questions assess the absolute frequency at which specific symptoms occur, thus reducing susceptibility of the questionnaire to mood fluctuations. Although EPIC has been developed to evaluate symptoms related to treatment for prostate cancer, it has also been validated for female patients with gynaecological malignancies and complications from radiotherapy.[15]

Since pelvic radiation injury often causes both urinary bladder and bowel symptoms, we asked patients to

answer the EPIC bowel domain, which consists of 14 items regarding bowel function and discomfort.

General health-related quality of life (HRQOL) was assessed with the generic 36-item Short Form (SF-36) questionnaire, which covers eight domains: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general health perception.[16] Answers are given on Likert scales. Results are presented both as a total score and subscores for each domain, which reflect the mean of the items included in the respective score. A lower value indicates a lower level of functioning and therefore a lower quality of life.

The diagnosis of late radiation cystitis was made by a urologist (KMH, PL, MV, LS, and OE) on the basis of medical history, findings at cystoscopy, and exclusion of other causes. Although this praxis was used from the start of the study (ie, the urologist judged that late radiation cystitis was the most probable cause for the patient's symptoms before inclusion), it was added as an explicit inclusion criterion by the steering committee through an amendment of the protocol on May 1, 2014. To minimise variation between examiners, all cystoscopies were performed by study-specific urologists (KMH, PL, MV, LS, and OE) and completed according to a detailed macroscopic evaluation protocol. The Radiation Therapy Oncology Group's Late Radiation Morbidity Grading Scheme (LRMGS) for the urinary bladder was used to assess epithelial atrophy, telangiectasia, haematuria, bladder capacity, and presence of necrosis or ulcerations. Grade 0 indicates normal findings at cystoscopy, whereas pathology is graded from 1 to 4. The final grade was determined by a blinded and independent examiner, using a transcript of the urologist's reports. Two to four mucosal cold biopsies were taken during cystoscopy in all patients unless this was judged to be inappropriate due to risk of bleeding or patient disapproval. The biopsy sites were pinpoint cauterised to avoid bleeding, and the biopsies stored for future histopathological analyses.

Safety assessments for the hyperbaric oxygen therapy group included recording of adverse events during hyperbaric oxygen therapy and a clinical examination, including laboratory assessment, after completion of hyperbaric oxygen therapy (visit 3). Patients were actively asked to report adverse events each day during the hyperbaric oxygen treatment period. Grading and classification of relation to the treatment was done by the local investigator. Ongoing adverse events at the end of the hyperbaric oxygen therapy period were followed until they resolved or until completion of visit 4. Serious adverse events were recorded for patients from both groups. A serious adverse event was defined as death, a life-threatening event, in-patient admission to hospital or extension of existing hospital stay, a persistent or substantial disability or incapacity, a congenital anomaly or birth defect, or an important medical event could be considered as a serious adverse event on the basis of appropriate medical judgement if it jeopardises the patient's health and might require medical or surgical intervention to prevent one of the listed adverse events.

All entries of the endpoint data were validated against source data and the audit trail was monitored independently by Gothia Forum, Gothenburg, Sweden.

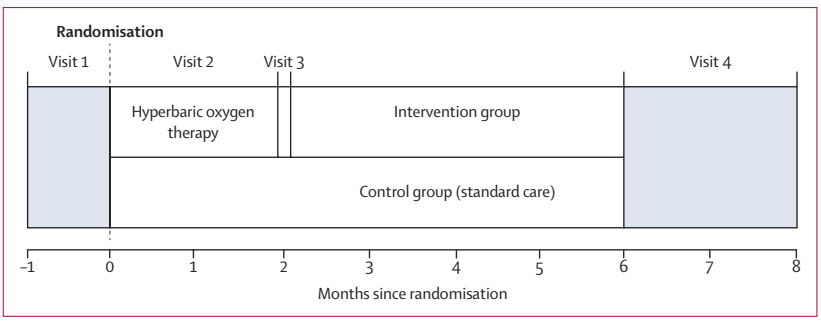

Figure 1: **Study design**
Randomisation was done directly after screening, at month 0. Hyperbaric oxygen therapy was given to the intervention group only (visit 2). A safety visit (visit 3) was done directly after the last hyperbaric oxygen therapy and only for the hyperbaric oxygen therapy group. Visit 4 was done 6–8 months after randomisation (ie, approximately 4–6 months after completion of hyperbaric oxygen therapy). Visit 1 and visit 4 were identical for the two groups. After completion of visit 4, all patients in the standard care group were offered hyperbaric oxygen therapy.

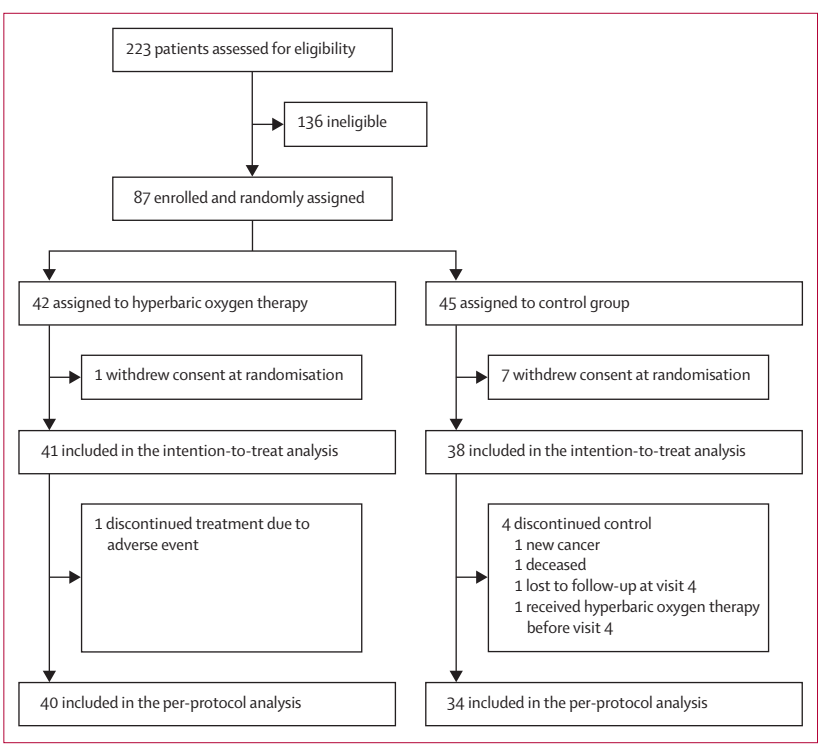

Figure 2: **Trial profile**
Patients in the standard care group were offered hyperbaric oxygen therapy after completion of visit 4 (ie, after the primary endpoint had been assessed).

Outcomes

In the predefined study protocol, the primary outcome was absolute change in EPIC urinary total score.

	Hyperbaric oxygen therapy group (n=41)	Standard care group (n=38)
Patient characteristics		
Age, years	64·0 (13·6), 41	64·8 (10·7), 38
Sex		
Men	29 (71%)	28 (74%)
Women	12 (29%)	10 (26%)
Smoking	2 (5%)	5 (13%)
Other nicotine use*	3 (7%)	2 (5%)
Previous invasive surgery†	19 (46%)	19 (50%)
Haematuria score		
Nil	18 (44%)	19 (50%)
Trace	2 (5%)	2 (5%)
+	3 (7%)	3 (8%)
++	8 (20%)	4 (11%)
+++	10 (24%)	10 (26%)
Localisation of cancer		
Cervix	10 (24%)	8 (21%)
Prostate	27 (66%)	27 (71%)
Rectum	3 (7%)	0
Uterus	0	2 (5%)
Other	1 (2%)	1 (3%)
Treatment of cancer‡		
Time from radiotherapy to inclusion, years	4·4 (5·1), 41	4·1 (3·4), 36
Time from debut of symptoms to inclusion, years	3·1 (4·8), 41	2·8 (2·8), 36
External radiation dose, Gy	63·8 (12·2), 40	63·5 (10·7), 36
Brachytherapy	12 (29%)	13 (34%)
Brachytherapy, Gy	21 (6·5), 10	18·2 (5·2), 12
Total combined radiation dose, Gy	79·5 (8·8), 10	69·1 (9·5), 12
Chemotherapy	12 (29%)	14 (37%)
Medical history and medications§		
Other disease, apart from cancer	33 (80%)	30/36 (83%)
Cardiac disorders	13 (32%)	6/36 (16%)
Hypertension	17 (41%)	18/36 (50%)
Respiratory disorder	6 (15%)	4/36 (11%)
Diabetes mellitus	2 (6%)	7/36 (19%)
Nervous system disorder	4 (10%)	5/36 (14%)
Depression	3 (7%)	2/36 (6%)
Any medication	26 (63%)	27 (71%)
Anticoagulant medicine (aspirin, clopidogrel, ticagrelor)	1 (2%)	2 (5%)
Medication for urinary urgency and incontinence (fesoterodine, mirabegron, tolterodine)	5 (12%)	2 (5%)

Data are n (%); n/N (%); or mean (SD), N. *Snus or nicotine chewing gum. †Pelvic surgery for malignant disease or surgery to the lower urinary tract for any reason. ‡Data missing for some patients, for reasons including inaccessible data due to older medical journal systems. §Two patients in the standard care group answered the question "Other disease, apart from cancer?" with "Yes", but no additional diagnosis was entered, therefore they were treated as missing data.

Table 1: **Patient characteristics**

Secondary outcomes were changes in SF-36 total and domain scores, histological changes in urinary bladder biopsies, and changes of LRMGS grades (referred to as Radiation Therapy Oncology Group grades in the protocol). In the statistical analysis plan, relative change in EPIC urinary total score, absolute change in EPIC bowel total score, and EPIC urinary domain scores were added as secondary outcomes before writing of the statistical analysis plan and assessment of the data. Changes in LRMGS grade were changed from a secondary outcome in the protocol to exploratory outcomes in the statistical analysis plan. Of the secondary endpoints, results for histological changes in urinary bladder biopsies will be reported separately.

Statistical analysis

The target sample size was calculated to detect an absolute change of 15 points in the EPIC urinary domain total score by visit 4, 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 (ie, 80 patients overall). Post-hoc (ie, during the study and compilation of the statistical analysis plan), we defined a minimal clinically important difference to be 0·5 SD of the EPIC urinary total mean score at visit 1.[17,18]

Outcome measures are presented for the intention-to-treat population, which included all randomly assigned patients, except those who withdraw consent immediately after randomisation. Analyses were also done in the per-protocol population, which included all participants who had been randomly assigned who had no major protol violations.

All analyses were done by the research group with the assistance of professional experts in medical statistics at Statistiska Konsultgruppen, Gothenburg, Sweden. Tests were two-tailed and done at a 0·05 significance level. Confidence intervals are presented at the 95% level. Analyses were done with SAS version 9.2. Missing data were not replaced.

The difference in EPIC urinary total score changes between the groups was tested for normality and skewness with Q–Q plots and Kurtosis, and statistical inference with Student's two-sample *t* test. Comparisons of the changes in EPIC subscores and SF-36 scores between groups were done with Fisher's non-parametric permutation test. When variances were not equal (p>0·05) the SD was based on Satterthwaite's approximation, otherwise the SD was based on the pooled SD. Changes in LRMGS grades were assessed using the Mantel-Haenszel χ^2 test for comparison between groups and the Sign test for comparison within groups. Also, baseline variables that could influence the association between the two groups on primary efficacy variable was included in linear interaction analyses with treatment. A post-hoc ANCOVA analysis was used to test the effect of the differences in baseline EPIC urinary total scores on the results.

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 is available in the appendix (pp 7–66), and the statistical analysis plan is available online.

Role of the funding source

The funders had no influence on the design and conduct of the study, and had no role in the collection, analysis, and interpretation of data, or in the writing of the manuscript. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

Of 223 patients screened between May 9, 2012, and Dec 20, 2017, 136 (61%) were ineligible for inclusion (figure 2; appendix p 1). After completion of baseline assessments, 87 patients were enrolled and randomly assigned to either hyperbaric oxygen therapy (42 patients) or control (45 patients). One (2%) patient in the hyperbaric oxygen therapy group and seven (16%) patients in the standard care group withdrew consent directly after randomisation, leaving 41 patients who received hyperbaric oxygen therapy and 38 who received standard care in the intention-to-treat analysis. EPIC and SF-36 scores at visit 1 and the characteristics of randomly assigned patients not included in intention-to-treat analyses are available in the appendix (p 2). In the per-protocol analysis, four further patients from the standard care group were excluded before visit 4 (one died, one was lost to follow-up, one was diagnosed with a new cancer, and one patient in the standard care group was unintentionally treated with hyperbaric oxygen therapy, and one patient in the hyperbaric oxygen therapy group was excluded due to discontinuation of therapy due to an adverse event). Hence, the per-protocol population included 40 patients in the hyperbaric oxygen therapy group and 34 patients in the standard care group.

All but one patient in the standard care group accepted and completed hyperbaric oxygen therapy after visit 4 (figure 1). RICH-ART closed enrolment on Dec 31, 2017; the last follow-up data will be compiled in 2023.

Demographics and disease characteristics were similar in both groups (table 1). Median time from randomisation to visit 4 was 234 days (IQR 210–262) in the hyperbaric oxygen therapy group and 217 days (195–237) in the standard care group.

EPIC urinary total score at visit 1 was normally distributed and without skewness (data not shown). At visit 4, the mean EPIC urinary total score in the hyperbaric oxygen therapy group had increased by 17·8 points (SD 18·4), compared with 7·7 points (15·5) in the standard care group. The difference between group means in the intention-to-treat population was 10·1 points (95% CI 2·2–18·1; p=0·013; figure 3, table 2).

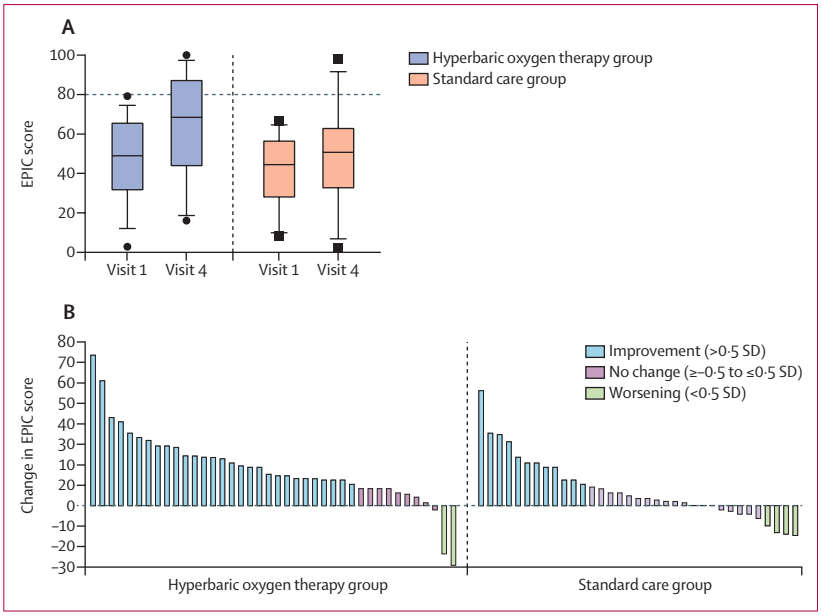

Figure 3: **EPIC urinary domain total score and individual change**
(A) Changes in EPIC score between visit 1 and visit 4 in each group. Group mean is shown with a line, and whiskers represent the the 5-95th percentiles. Outliers are marked with a solid circle or square. The dotted line at a score of 80 indicates the cut-off for inclusion. (B) Individual changes in EPIC score between visit 1 and visit 4, according to the minimal clinically important difference of 0·5 SD of the EPIC urinary total mean score at visit 1 (which was defined post hoc). The patient in the standard care group who improved by more than 40 points unintentionally received hyperbaric oxygen therapy before evaluation at visit 4. EPIC=Expanded Prostate Index Composite.

The per-protocol analysis for EPIC urinary total score showed a difference in group means of 11·4 points (95% CI 3·5–19·2; p=0·0047). All per-protocol analyses are provided in the appendix pp 3–6. EPIC subscores improved significantly in the hyperbaric oxygen therapy group compared with the standard care group for the urinary domains of bother and incontinence and for the EPIC bowel scores. No other changes in urinary domain subscores reached statistical significance (table 2). The median bladder capacity at visit 1 was 300 mL (IQR 192–375) in the hyperbaric oxygen therapy group and 300 mL (200–400) in the standard care group. At visit 4, the mean bladder capacity was 300 mL (IQR 240–390) and 260 mL (200–362), respectively.

Potentially confounding factors that could influence EPIC urinary total score were assessed in a post-hoc interaction analysis: invasive surgery (p=1·0), body-mass index (p=0·78), sex (p=0·77), age (p=0·33), and time from radiotherapy to inclusion (p=0·20).

Individual changes in EPIC urinary domain subscores are shown in figure 3B. With an SD of 18 for EPIC urinary total score for all patients at baseline (data not shown), the minimal clinically important difference was calculated post hoc as 9 points on the EPIC total urinary score. Categorised according to this minimal clinically important difference, in the hyperbaric oxygen therapy group 29 (73%) of 40 patients improved (one patient was missing data at visit 4), nine (23%) had no change, and

For the **statistical analysis plan** see https://clinicaltrials.gov/ProvidedDocs/23/NCT01659723/SAP_000.pdf

	Hyperbaric oxygen therapy group	p value within group	Standard care group	p value within group	p value between groups	Mean difference between groups (95% CI)
Visit 1 (baseline)						
Number of patients	41	..	38	..	..	..
EPIC						
Urinary total	48·2 (19·0)	..	41·6 (17·2)	..	0·11	..
Urinary function	56·0 (23·0)	..	48·6 (22·5)	..	0·16	..
Urinary bother	42·7 (19·7)	..	36·7 (16·6)	..	0·23	..
Urinary incontinence	49·4 (32·6)	..	36·4 (27·7)	..	0·12	..
Urinary irritable/obstruction	50·1 (19·8)	..	46·0 (18·6)	..	0·38	..
Bowel total	60·4 (21·0)	..	63·6 (22·6)	..	0·73	..
SF-36						
Physical functioning	72·4 (20·6)	..	68·2 (25.6)	..	0·43	..
Role limitations due to physical health	39·6 (41·1)	..	34·2 (37·9)	..	0·57	..
Role limitations due to emotional problems	61·0 (42·1)	..	53·5 (40·7)	..	0·43	..
Energy/fatigue	47·2 (23·5)	..	44·7 (23·0)	..	0·65	..
Emotional wellbeing	72·7 (18·8)	..	70·1 (21·6)	..	0·58	..
Social functioning	69·8 (27·0)	..	62·2 (30·3)	..	0·24	..
Pain	65·5 (27·1)	..	53·6 (25·7)	..	0·053	..
General health	52·9 (20·7)	..	55·0 (22·6)	..	0·68	..
Visit 4						
Number of patients	40	..	35	..	..	..
EPIC						
Urinary total	65·5 (24·6)	..	48·8 (24·2)	..	0·0044	..
Urinary function	69·1 (28·8)	..	52·8 (26·9)	..	0·015	..
Urinary bother	62·9 (24·6	..	45·9 (23·9)	..	0·0041	..
Urinary incontinence	60·4 (36·7)	..	36·1 (29·9)	..	0·0031	..
Urinary irritable/obstruction	69·2 (22·7)	..	56·0 (24·6)	..	0·020	..
Bowel total	73·5 (16·4)	..	67·5 (23·2)	..	0·20	..
SF-36						
Physical functioning	76·7 (22·6)	..	66·3 (26.0)	..	0·074	..
Role limitations due to physical health	51·9 (44·6)	..	34·3 (42·5)	..	0·087	..
Role limitations due to emotional problems	56·4 (45·3)	..	52·4 (45·2)	..	0·69	..
Energy/fatigue	53·6 (21·9)	..	45·1 (27·7)	..	0·15	..
Emotional wellbeing	76·2 (17·6)	..	70·9 (23·9)	..	0·28	..
Social functioning	75·6 (26·9)	..	60·4 (31·4)	..	0·029	..
Pain	73·4 (24·9)	..	58·9 (29·3)	..	0·028	..
General health	62·1 (21·0)	..	50·9 (22·7)	..	0·033	..
Change from visit 1 to visit 4						
EPIC						
Urinary total	17·8 (18·4)	<0·0001	7·7 (15·5)	0·0049	0·013	−10·1 (−18·1 to −2·2)
Post-hoc analysis of urinary total adjusted means (ANCOVA)	18·0 (12·4–23·5)	<0·0001	7·5 (1·7–13·4)	0·0049	0·012	−10·4 (−18·5 to −2·3)
Urinary function	13·8 (19·8)	<0·0001	5·6 (15·2)	0·036	0·052	−8·2 (−16·6 to 0)
Urinary bother	20·7 (20·1)	<0·0001	9·2 (17·7)	0·0028	0·012	−11·5 (−20·3 to −2·7)
Urinary incontinence	12·8 (18·5)	<0·0001	0·7 (14·8)	0·78	0·0031	−12·1 (−19·9 to −4·3)
Urinary irritable/obstruction	19·6 (21·8)	<0·0001	10·4 (18·6)	0·0010	0·059	−9·19 (−18·64 to 0·22)
Bowel total	13·2 (17·3)	<0·0001	4·9 (12·7)	0·033	0·024	−8·33 (−15·54 to −1·15)

(Table 2 continues on next page)

	Hyperbaric oxygen therapy group	p value within group	Standard care group	p value within group	p value between groups	Mean difference between groups (95% CI)
(Continued from previous page)						
SF-36						
Physical functioning	4·6 (13·8)	0·045	−1·6 (15·0)	0·55	0·075	−6·19 (−12·87 to 0·49)
Role limitations due to physical health	12·2 (48·6)	0·13	−2·1 (34·0)	0·72	0·15	−14·3 (−33·9 to 5·1)
Role limitations due to emotional problems	−5·1 (46·2)	0·49	−3·8 (47·7)	0·64	0·90	1·32 (−20·46 to 23·10)
Energy/fatigue	7·2 (18·4)	0·021	1·1 (14·4)	0·65	0·13	−6·04 (−13·72 to 1·65)
Emotional wellbeing	3·8 (18·1)	0·20	0·6 (13·3)	0·81	0·41	−3·22 (−10·64 to 4·19)
Social functioning	5·4 (26·7)	0·21	−0·357 (21·964)	0·92	0·32	−5·81 (−17·14 to 5·62)
Pain	8·3 (23·7)	0·034	7·1 (22·9)	0·072	0·85	−1·19 (−12·04 to 9·67)
General health	9·4 (16·5)	0·0012	−3·9 (14·3)	0·12	0·0006	−13·2 (−20·4 to −6·0)

Data are presented as mean (SD), or mean (95% CI). One patient in the hyperbaric oxygen therapy group and three in the standard care group had missing data at visit 4. EPIC=Expanded Prostate Index Composite. SF-36=36-item Short Form.

Table 2: **EPIC and SF-36 scores**

two (5%) worsened. Further analysis of these two patients showed that EPIC urinary total scores at visit 1, visit 4, and 1-year follow-up were 59, 35, and 100 for one patient and 48, 19 and 52 for the other patient. In the standard care group, 12 (34%) of 35 patients improved (three patients were missing data at visit 4), 19 (54%) had no change, and four (11%) worsened. The number of patients who scored 80 or higher on EPIC at visit 4 was 16 (40%) of 40 in the hyperbaric oxygen therapy group and three (9%) of 35 in the standard care group.

By contrast with the standard care group, mean SF-36 scores increased significantly within the hyperbaric oxygen therapy group from visit 1 to visit 4 in four of the eight domains, with a significant improvement in the hyperbaric oxygen therapy group for general health (p=0·0006; table 2). In the standard care group, mean SF-36 scores did not increase significantly for any domain.

The urological assessment at visit 1 showed higher LRMGS grades in the hyperbaric oxygen therapy group than in the standard care group (p=0·068; figure 4). At visit 4, 25 (64%) of 39 patients in the hyperbaric oxygen therapy group (two of 41 patients had missing data at visit 4) had improved grades, 11 (28%) had unchanged grades, and three (8%) had worsened grades. In the standard care group, six patients (18%) of 34 patients (four patients in the group had missing data at visit 4) had improved grades, 18 (53%) had unchanged grades, and ten (29%) had worsened grades (Mantel-Haenszel χ^2 test for difference between groups, p=0·0012). Results on histological changes in urinary bladder biopsies have yet not been analysed and will be published separately.

Regarding safety and tolerability, all patients in the hyperbaric oxygen therapy group complied with the predefined hyperbaric oxygen therapy protocols, and no dose adjustments were required. We recorded 43 adverse events affecting 17 (41%) of 41 patients in the hyperbaric oxygen therapy group (table 3). Difficulty equalising pressure in the middle ear while pressurising the hyperbaric chamber, thus causing temporary pain, constituted nine adverse events, and affected six (15%) of 41 patients. Signs of barotrauma were seen in four (10%) of 41 patients, and paracentesis of the tympanic membrane was necessary in one (2%) of 41 patients. Hyperoxia-induced transient myopia with changes in

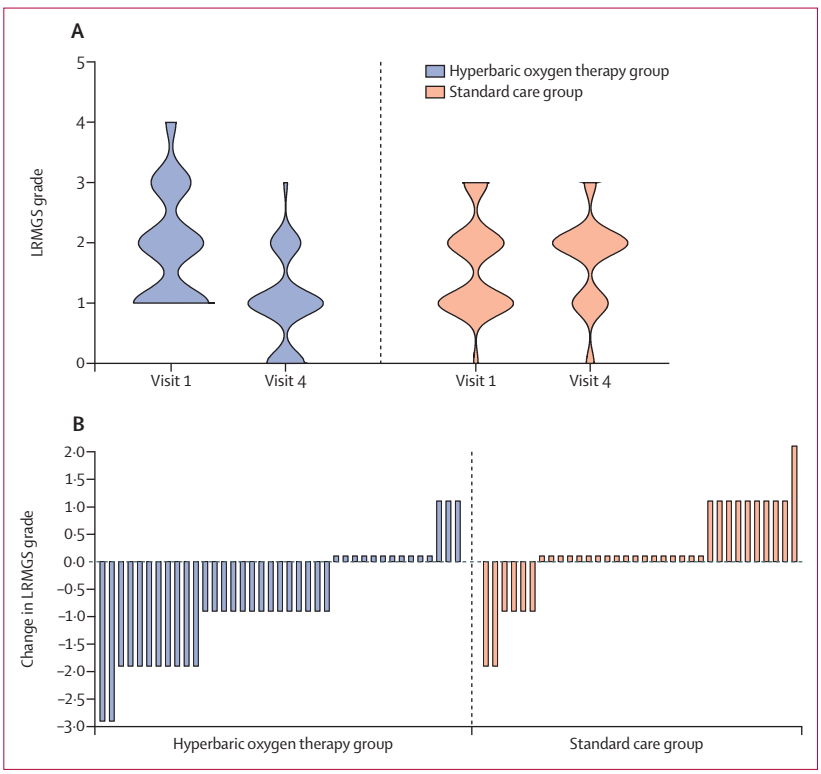

Figure 4: **Urological assessment and individual change in LRMGS grade**
(A) Change in LRMGS grade between visit 1 and visit 4 in each treatment group. (B) Individual changes in LRMGS grade between visit 1 and visit 4. A lower LRMGS grade means fewer pathological findings. Thus, a negative change represents improvement. LRMGS=Late Radiation Morbidity Grading Scheme.

	Hyperbaric oxygen therapy group (n=41)	Standard care group (n=38)
Patients with any adverse event	17 (41%)	1 (3%)
Grade 1–2	17 (41%)	0
Ear: ear pain	6 (15%)	0
Eye: myopia	5 (12%)	0
Injury: barotrauma	4 (10%)	0
Grade 3–4	0	0
Grade 5	0	1 (3%)
Cardiac: cardiac failure	0	1 (3%)

Adverse events are sorted by grade and organ class (MeDRA preferred term). Adverse events of grade 1–2 are only listed for the respective organ class if they affected 10% or more of the patients in either group. All grade 3–5 adverse events are listed. Only serious adverse events were recorded for the standard care group.

Table 3: **Adverse events**

vision was recorded in five (12%) of 41 patients. Both ear and vision problems were clearly related to hyperbaric oxygen therapy. One patient with Leber's hereditary optic neuropathy discontinued hyperbaric oxygen therapy due to visual disturbances. Although the most probable cause was hyperoxia-induced transient myopia, the patient feared additional and persisting visual impairment and discontinued treatment. One patient had a panic attack at one occasion, which was related to pre-existing claustrophobia. There was no clear relation to hyperbaric oxygen therapy for the remaining adverse events (sevens infections [six grade 1 and one grade 3], five transient muscle cramps or pain [grade 1], three haematuria [two grade 1 and one grade 3], two diarrhoea [grade 1], one fatigue [grade 1], one nausea [grade 1], and one headache [grade 1]). Fatigue, nausea, and headache, were all detected in different individuals, and were thus not interpreted as symptoms of oxygen toxicity. One patient in the standard care group died during the study period due to sepsis and cardiac failure unrelated to the study.

At baseline, there was a small difference in EPIC urinary total score between the randomisation groups (48·2 points [SD 19·0] in the hyperbaric oxygen therapy group *vs* 41·6 points [17·2] in the standard care group). Although this difference was not significant (p=0·11), a post-hoc ANCOVA analysis with adjusted means was done to control for the effect of difference in baseline EPIC urinary total score. This analysis rejected the null hypothesis for the primary endpoint (ie, patient-perceived urinary total symptoms; p=0·012)

Discussion

To our knowledge, RICH-ART is the first randomised, controlled trial of hyperbaric oxygen therapy in late radiation cystitis to have assessed a broad range of symptoms associated with late radiation tissue injuries. Our findings show that hyperbaric oxygen therapy significantly alleviated patient-perceived symptoms of late radiation cystitis and improved HRQOL. Furthermore, macroscopic changes of the urinary bladder associated with late radiation tissue injuries were reduced when assessed by cystoscopy.

The enrolment period for this trial was 5 years and 8 months. During this time, new radiotherapy treatment modalities have been developed, aiming to personalise radiotherapy on the basis of individual radiosensitivity.[19] New treatment modalities might reduce the incidence of late radiation cystitis, but the number of patients that are affected by late radiation cystitis is still relatively high and remains a challenge for health-care systems.[20] Onset of late radiation cystitis can occur many years after radiation, and thus effective treatment remains a highly relevant clinical issue, despite ongoing improvements in the field of radiotherapy.

Numerous reports have demonstrated positive outcomes after hyperbaric oxygen therapy for late radiation cystitis, but prospective evidence is limited, mostly originating from small, single-centre studies.[10,12,21] In a previous prospective, single-centre, cohort study on radiation-induced cystitis and proctitis, we found a mean increase in EPIC urinary total scores of 15 points 6–12 months after hyperbaric oxygen therapy. In that study, 22 (76%) of 29 patients with a baseline urinary EPIC score less than 80 showed an increase in EPIC scores after hyperbaric oxygen therapy.[10] In RICH-ART, the mean improvement in EPIC urinary total score was higher (17·8 [SD 18·4]) in the hyperbaric oxygen therapy group compared with patients in the control group, who received standard care (7·7 points [SD 15·5]), and 29 (73%) of 40 patients treated with hyperbaric oxygen therapy increased their score by more than 9 points (ie, minimal clinically important difference used for EPIC urinary total score). Previous studies[10,14] have shown an SD of 13·3–18·6 for EPIC urinary total score with a minimal clinically important difference of 9 points or less. In a 2018 study[18] on the extent to which changes in HRQOL are clinically relevant for patients, a minimal clinically important difference of 10 points was suggested for the EPIC urinary total score. Changes in the EPIC subscores indicate that functional aspects of late radiation cystitis and the degree of perceived bother both improved after hyperbaric oxygen therapy.

We observed variable individual responses to hyperbaric oxygen therapy, with some patients not improving and two even deteriorating (figure 3). A proportion of non-responders is to be expected in practically any form of medical treatment and has been previously reported in hyperbaric oxygen therapy for late radiation cystitis, but the underlying causes remain unclear.[3,8] Two patients in the hyperbaric oxygen therapy group worsened, rather than improved: one was diagnosed with a urethral stricture, and another with severe urinary incontinence after radical prostatectomy during the hyperbaric oxygen therapy phase. Symptoms resolved in both patients after surgery, consisting of urethrotomy and artificial sphincter

implantation, respectively. At 1 year follow-up, both patients had improved EPIC urinary total scores.

Our inclusion criteria, based on both clinical findings and cystoscopy, aimed to ensure selection of patients with late radiation cystitis as the most likely and relevant cause for their urinary symptoms. However, we cannot exclude that other pathology was present and affected the urinary system in some patients. EPIC has been reported to be 89·5 points (SD 11·2) in healthy controls who have not previously received pelvic radiotherapy.[14] By using an EPIC urinary total score of less than 80 as an inclusion criterion, we avoided both a scale-related ceiling effect and the inclusion of patients with symptoms so mild that they would be easily indiscernible from age-related urinary problems.[22] The pathophysiological changes induced by radiotherapy evolve over time and the dose and timing of hyperbaric oxygen therapy might also important to the individual response to the treatment. An increased proportion of patients respond to hyperbaric oxygen therapy if treated within 6 months from onset of haematuria or within a short time from radiotherapy.[23]

Although previous studies have shown that a decreased time from radiotherapy to hyperbaric oxygen therapy seems to affect outcome positively, patients with a long history of radiation cystitis might still respond to hyperbaric oxygen therapy. This scenario has recently been described in a study into haemorrhagic cystitis with a mean interval from radiotherapy to hyperbaric oxygen therapy of 24·7 months (range 2–212), translating to more than 17 years from radiotherapy to hyperbaric oxygen therapy for some patients.[11] In our interaction analysis, baseline variables that could influence the association between the two groups on primary efficacy outcome was included in a linear interaction analysis with treatment. Although none of the variables reached the predefined cutoff for further analysis ($p<0·1$), time from radiation to hyperbaric oxygen treatment seems to warrant further analysis when the pooled data after treatment from both groups are available. This finding underscores the need for future studies into the timing from radiotherapy to eventual receipt of hyperbaric oxygen therapy.

Although late radiation cystitis is chronic in nature, the intensity of symptoms often varies over time.[4] This fact might explain why a few patients in the standard care group improved without hyperbaric oxygen therapy. The erroneous, premature treatment with hyperbaric oxygen therapy and the wrong timing of visit 4 which occurred for one patient in the standard care group did not affect the significance of the overall result. The per-protocol analysis shows that exclusion of this patient would have resulted in an outcome even more favourable for hyperbaric oxygen therapy. Strict adherence to protocol is necessary to obtain reliable results, but our opinion is that this error on our behalf did not affect the validity of our results.

In line with reduced urinary symptoms, macroscopic evaluation of the urinary bladder showed a notable improvement after hyperbaric oxygen therapy. This finding concurs with previous reports on hyperbaric oxygen therapy and haemorrhagic radiation cystitis.[21,24] The macroscopic changes seen in the urothelium are caused by cellular and biochemical processes induced by hyperbaric oxygen therapy.[25] We have collected biopsy samples from the urinary bladders at both visits for future analysis of histological, cytological, and biochemical markers, and will publish these findings separately.

The effect of hyperbaric oxygen therapy on HRQOL has been investigated to a small extent in patients with late radiation cystitis. We identified one study, based on a small cohort of 11 patients with little statistical power, describing the use of the generic SF-36 questionnaire, in which a significant improvement in one single domain was found.[26] In our study, scores improved in the hyperbaric oxygen therapy group in four domains, including physical and individual quality-of-life aspects (physical functioning, energy, bodily pain, and general health); the magnitudes of these changes correspond to small or moderate effect sizes.[27] The more complex social–interactive and emotional domains did not improve (role limitations—physical, role limitations—emotional, emotional wellbeing, and social functioning). It might take a longer time for the social and psychological improvements to become evident in these patients' lives than the follow-up of this study. However, the relatively small changes might also illustrate the poor responsiveness of generic HRQOL tools in repetitive assessment of patients with a specific and complex condition. Further research is clearly needed on the effect of hyperbaric oxygen therapy on HRQOL in patients with late tissue injuries from pelvic irradiation, and we are aware of one ongoing study on this issue (NCT03570229).

Many patients with late radiation cystitis also have symptoms from adjacent organs such as the rectum or genitalia. We included the bowel part of EPIC and noted a significant improvement in patient-reported symptoms with hyperbaric oxygen therapy. This finding illustrates that the effects of hyperbaric oxygen therapy are not organ specific and gives further support to the use of hyperbaric oxygen therapy for radiation-induced proctitis.[28] We did not use the EPIC sexual domain, because it is designed for male patients only, but we see a need for future studies to address this important area.

The reported incidence of adverse events related to hyperbaric oxygen therapy varies greatly. In our study, minor barotrauma of the middle ear and oxygen-induced myopia were predominantly reported, both of which are manageable and usually reversible conditions. On the basis of on the low severity and temporary character of adverse events related to hyperbaric oxygen therapy reported in our and other studies, we therefore characterise hyperbaric oxygen therapy as a safe and well-tolerated treatment.[29]

The number of sessions of hyperbaric oxygen therapy provided to patients varied among the participating centres because of differences in local policies, routines, and reimbursement models. Because our study was not designed to explore dose–response associations, the steering committee decided on a pragmatic protocol to allow the number of sessions to vary between 30 and 40 in the interest of recruitment. Although 30 sessions seems to have achieved a clinically relevant effect, we cannot rule out that the result might improve further with a higher number of treatments. However, due to the small size of our study, this question cannot be analysed with enough statistical power at this stage. We will address these questions when the pooled EPIC data for 4–6 months after hyperbaric oxygen therapy and 1-year follow-up are available for both the hyperbaric oxygen therapy group and the standard care group. The study protocol also allowed for small local differences in administration of hyperbaric oxygen therapy. Some centres used one or two air breaks, in which the delivery of oxygen is paused for 5 min to reduce the risk of oxygen toxicity. Other centres used a slightly shorter treatment duration with no air breaks (ie, 10 min shorter treatment duration without air breaks compared with treatment duration with air breaks). The total dose of oxygen delivered at each session was, however, similar (data not shown).

Patients were referred to the hyperbaric centre predominantly from urologists and general practitioners. In most patients, other treatments or medication had been attempted (data not shown). We did not control for previous or current therapies used to alleviate symptoms of late radiation cystitis, but new treatment modalities were restricted to those deemed to be vital for the patient during the study as determined by the urologist. Hyperbaric oxygen therapy was thus added to standard care for patients in the intervention group; although this study design makes it impossible to compare the effectiveness of hyperbaric oxygen therapy to other therapies, our findings support the notion that there is a beneficial effect of adding hyperbaric oxygen therapy to currently used treatment regimens.

Our study was designed as a pragmatic trial, with wide inclusion criteria. Patients who were permanently catheterised were excluded, because most answers on the urinary symptom questionnaire were not applicable to them. Despite exclusion of patients with the mildest symptoms and those with very severe symptoms (ie, EPIC score >80 or haematuria requiring transfusion), the wide range of EPIC scores at baseline suggests that our study covered a broad spectrum of clinical manifestations of late radiation cystitis and should have general validity for this condition.

Patients with severe bleeding who required multiple transfusions were not eligible for inclusion, because it was deemed unethical to withhold hyperbaric oxygen therapy. These patients require active and often invasive treatment interventions, which would interfere with the study protocol and make interpretation of EPIC scores impossible. However, hyperbaric oxygen therapy is, in our clinical praxis, often used for these patients with good effect and is by no means contraindicated.

Sham treatment has been used in previous studies of hyperbaric oxygen therapy, but requires extensive resources and recruitment to such trials has been proven to be a major challenge. Patients and referring physicians are often reluctant to risk time-consuming placebo treatment for several weeks, especially for conditions and in hospitals where hyperbaric oxygen therapy is a relatively established treatment option. Randomised controlled trials of hyperbaric oxygen therapy have been stopped prematurely due to low recruitment, as was the case for the HORTIS-III trial (NCT00134628) that had the same objective as ours. The role of sham treatment should also be considered in view of findings from a study[30] of hyperbaric oxygen therapy for late radiation bowel dysfunction; neither the hyperbaric oxygen therapy group nor the sham group showed improvement in their symptoms, by contrast with earlier evidence, questioning the relevance of a placebo effect several months after a therapeutic procedure has been applied.[30] Sham treatment was not used in RICH-ART and patients were not masked to the intervention. Because of this study design, it was deemed unethical to have a urologist masked to treatment allocation perform the second cystoscopy at visit 4. However elegant, it would have relied on patients concealing their intervention type to the urologist—a demand we considered unreasonable to make.

Clinically evident effects of hyperbaric oxygen therapy, with symptomatic improvement of late radiation tissue injury-related symptoms, are usually not reported until the end of the treatment protocol. In our clinical experience, it can take 2–3 months after hyperbaric oxygen therapy before the effects of the treatment become apparent. This delay in clinical effects has also been observed in other conditions treated with hyperbaric oxygen therapy.[31] Therefore, we waited 4–6 months after completion of hyperbaric oxygen therapy (6–8 months after randomisation) before making the final comparative assessments at visit 4. Our study was an open-label trial, and at all participating centres except for one (Turku, Finland) hyperbaric oxygen therapy is offered routinely as an option for the treatment of late radiation tissue injuries. This study design meant that patients randomly assigned to the standard care group (ie, no hyperbaric oxygen therapy) had the possibility to decline further participation in the study and thereby receive hyperbaric oxygen therapy earlier than if they had remained in the study. The lack of masking to group allocation could thus have contributed to the disproportionate loss of patients in the standard care group. The extent of drop-out due to this reason would most likely be even higher with further delay of hyperbaric oxygen therapy (eg, due to longer follow-up), causing extensive recruitment problems.

We based our sample size calculations on data available when the protocol was compiled in 2010 and conclude that we overestimated the standard deviation (SD 23) and the minimal clinically important difference (15 points) in our calculations.[10,18] With our new data we conclude that a SD of around 20 seems more relevant for future sample size calculations.

All but one participant in the standard care group accepted hyperbaric oxygen therapy after visit 4. These patients, together with all patients in the hyperbaric oxygen therapy group, will be analysed further for outcomes after hyperbaric oxygen therapy when follow-up is complete. Hence, the group available for long-term follow-up in future analyses will constitute patients from both the hyperbaric oxygen therapy group and the standard care group. We also intend to analyse cofounding factors and dose–response aspects when these data become available. Because evidence on the long-term outcome after hyperbaric oxygen therapy is scarce, we have included the patients in a 5-year follow-up programme as a post-study cohort.

Some issues warrant further discussion. It would have been scientifically more favourable to withhold hyperbaric oxygen therapy for the standard care group during the whole follow-up period of 5 years, but a delay of several years was not considered ethically or medically acceptable. In the standard care group, seven patients withdrew consent directly after randomisation, potentially because they did not receive prompt hyperbaric oxygen therapy. This factor illustrates a problem inherent to unblinded controlled studies, because group allocation might influence loss of data. Since these patients were excluded from the intention-to-treat analyses, a potential source of bias was introduced. However, EPIC and SF-36 scores and characteristics in both groups were similar at visit 1, indicating an even distribution. Another potential limitation is that smoking and smoking habits were not accounted for in this study. Besides representing a carcinogenic exposure, smoking is related to many harmful side-effects that might have affect overall treatment efficacy.

To conclude, our study shows a beneficial effect of hyperbaric oxygen therapy for late radiation cystitis on several urological symptoms and quality of life in both female and male patients. The treatment was safe and well tolerated. Hyperbaric oxygen therapy seems to have a place among treatment options for radiation-induced organ complications which until now has been limited to symptomatic modalities. New radiation modalities might also increase demand for therapies for radiotherapy-induced side-effects.[32] Further studies of microscopic changes and long-term effects are expected to answer some remaining questions.

Contributors

NO, FL, GV, PL, JM, and HS-L all 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, GV, OE, OH, FL, and OA enrolled patients at their respective sites. PL, MV, LS, and KMH made the cystoscopies and urological assessment of the participants. NO, BM, and AR drafted the manuscript. NO, BM, AR, OE, DG, FL, JM, KMH, PL, AK, and HS-L provided critical review of the article. All authors approved the final manuscript.

Declaration of interests

NO, HS-L, and PL report grants from Regional Research Fund VGR (Gothenburg, Sweden). NO and HS-L report grants from the regional Health Technology Assessment Centre at Sahlgrenska University, Gothenburg Sweden, and Lions Cancer Research Fund of Western Sweden, Gothenburg, Sweden, during the conduct of the study. NO reports being a Board member in MediCase AB since Feb 5, 2014. All other authors declare no competing interests.

Data sharing

The study protocol, statistical analysis plan, and informed consent form are available within the Article. Individual (deidentified) participant data that underlie the results reported in this article will be available beginning 9 months and ending 36 months after Article publication. However, data that are part of the follow-up or that are yet unpublished will not be shared before publication of this data. A full description of the intended use of the data must be sent to RICH-ART's steering committee for review and approval.

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