

Clinical Investigation: Normal Tissue

Hyperbaric Oxygen Treatment in Radiation-Induced Cystitis and Proctitis: A Prospective Cohort Study on Patient-Perceived Quality of Recovery

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Summary

In this prospective cohort study, the effects of hyperbaric oxygen treatment (HBOT) on patient-perceived symptoms of late radiation-induced cystitis and proctitis were studied, using the Expanded Prostate Index Composite score. In the majority (>75%) of patients, patient-perceived symptoms were alleviated after HBOT, an improvement that was sustained for at least 6 to 12 months. Twenty to 30 percent of patients reported only trivial symptoms after HBOT. Compliance with HBOT was high, and side effects were few.

Purpose: In this prospective cohort study, the effects of hyperbaric oxygen treatment (HBOT) were evaluated concerning patient-perceived symptoms of late radiation-induced cystitis and proctitis secondary to radiation therapy for pelvic cancer.

Methods and Materials: Thirty-nine patients, 35 men and 4 women with a mean age of 71 (range, 35-84) years were included after informed consent and institutional ethics approval. They had all been treated with radiation therapy for prostate (n=34), cervix (n=2), or rectal (n=3) cancer using external beam radiation at a dose of 25 to 75 Gy. Patients with hematuria requiring blood transfusion were excluded. The HBOT was delivered with 100% oxygen for 90 minutes at 2.0 to 2.4 atmospheres (ATA). Mean number of treatments was 36 (28-40). Symptoms were prospectively assessed using the Expanded Prostate Index Composite score before, during, and 6 to 12 months after HBOT.

Results: The HBOT was successfully conducted, and symptoms were alleviated in 76% for patients with radiation cystitis, 89% for patients with radiation proctitis, and 88% of patients with combined cystitis and proctitis. Symptom reduction was demonstrated by an increased Expanded Prostate Index Composite score in the urinary domain from 50 ± 16 to 66 ± 20 after treatment ($P < .001$) and in the bowel domain from 48 ± 18 to 68 ± 18 after treatment ($P < .001$). For 31% of the patients with cystitis and 22% with proctitis, there were only trivial symptoms after HBOT. The improvement was sustained at follow-up in both domains 6 to 12 months after HBOT. No severe side effects were observed related to HBOT, and treatment compliance was high.

Conclusions: HBOT can be an effective and safe treatment modality for late radiation therapy-induced soft tissue injuries in the pelvic region. © 2013 Elsevier Inc.

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Introduction

Despite continuous improvement in techniques administering radiation therapy, adverse effects are still common (1). The incidence of rectal and urinary bladder complications with late onset following curative doses of radiation therapy for cervical, uterine, prostate, or rectal cancer is reported to be 5% to 15% (2, 3).

The urinary bladder and the rectum are 2 major organs commonly affected by radiation to the pelvic region. Radiation injuries can be classified as acute (within weeks) or late (a few months up to 10 years or more) (4). Acute injury is considered to be caused by a cellular toxicity mediated by free radicals damaging cellular DNA (5), whereas the commonly accepted explanation of the late radiation therapy-induced injury is the development of an obliterative endarteritis (6). The clinical symptoms of the acute form are usually self-limiting and can be treated with simple, direct attempts to limit symptoms (as discussed subsequently), but the injury can sometimes persist and develop into a late injury (7). Late injury is often progressive and difficult to alleviate with conventional local treatment. Bleeding is common, sometimes requiring blood transfusions. Because of reduced capacity of the urinary bladder and rectum, urgency and frequent micturition and/or defecation are common. Furthermore, pain and discomfort in the pelvic area, as well as urinary or fecal incontinence, frequently occur. The severity of symptoms often results in restrictions of the patient's lifestyle, leading to a drastic decrease in quality of life (2, 8).

The conventional treatment of late radiation injuries to the bladder and/or rectum is to try to limit symptoms. Different means of surgical coagulation and installation of substances such as formalin, alun, and steroids in the rectum or the urinary bladder are often tried to stop bleeding or to reduce inflammation (2, 9-11). If the symptoms progress into more severe forms, the more radical treatment can be rectal or urinary diversion.

The use of hyperbaric oxygen treatment (HBOT) as a therapy modality of radiation-induced proctitis and cystitis is not new. Several studies have reported a positive effect of HBOT, but with a few exceptions, the studies are small, retrospective, lack a control group, and are not randomized (2).

The objective of this prospective cohort study was to assess whether HBOT could reduce patient-perceived symptoms of radiation-induced cystitis and proctitis, using Expanded Prostate Index Composite (EPIC) scores as a primary variable for evaluation (12).

Methods and Materials

Patient population

The study was approved by the Regional Ethical Board in Gothenburg and complies with the Helsinki declaration (International Conference on Harmonisation/Good Clinical Practice). Informed consent was obtained from all patients. The study was conducted between January 2008 and December 2011 at Sahlgrenska University Hospital/Östra. Inclusion criteria were as follows: diagnosis of late radiation-induced cystitis/proctitis made by a referring urologist or surgeon, based on medical history, symptoms (bleeding from the mucosa, pain in the pelvis region, incontinence, frequent and/or imperative urge for defecation and/or urination) and/or objective findings (macroscopically evident bleeding from the mucosa, telangiectasia, atrophy of the mucosa,

ulcers and signs of increased fibrosis, and indirect findings such as reduced bladder volume, residual urine, hematuria, microscopic findings of blood in feces, and reduced sphincter tonus). Exclusion criteria were severe claustrophobia, smoking, inability to follow simple instructions, pregnancy, and requirement of blood transfusions (Fig. 1). Patients with a urinary catheter were unable to answer the urinary domain of the EPIC questionnaire, and patients with intestinal diversion were unable to answer the bowel domain of the EPIC questionnaire. The data for these patients have been included and analyzed only in the domain in which they were able to give valid answers. Patient demographics and cancer management are shown in Table 1. Mean time from end of radiation therapy to urinary symptoms was 18 (0-120) months, with a median of 1.5 months, and mean time from end of radiation therapy to bowel symptoms was 5.5 (0-120) months with a median of 1.5 months. Although some patients had onset of symptoms within 6 months from radiation therapy (acute injuries), all patients included in the study had either persistent symptoms or relapse of symptoms >6 months after end of radiation therapy, hence defining them as late injuries.

HBOT study protocol

The time period from end of radiation therapy to start of HBOT had to exceed 6 months, thus minimizing the treatment of patients with acute injuries that might regress spontaneously. Most patients (n=35) were treated in a multiplace hyperbaric chamber, pressurized to 2.4 ATA, in which they were given 100% oxygen for 90 minutes. Four patients were treated in a monoplace chamber, pressurized to 2.0 ATA, where they were given 100% oxygen for 90 minutes. The choice of hyperbaric chamber was based on patient preference. The treatments were given once daily, 5 days weekly. The initial number of prescribed treatments was 30, given within 45 days. Following the initial treatment, patient response was assessed by a hyperbaric medicine specialist (N.O. or P.A.) and categorized in 1 of 4 categories: healed, improved, unchanged, or worse. Patients in the group "improved" were offered an additional 10 treatments, which generally were administered within 2 months from the end of the initial treatment sequence. Treatment was stopped for patients falling into any of the other 3 groups.

Collection of data

Patients were evaluated with a Swedish translation of EPIC (12, 13). At the time of the initial assessment, demographics, comorbidity, medications, and cancer treatment history were recorded. Patients were asked to fill out the EPIC form directly after the last HBOT and at follow-up 6 to 12 months after end of HBOT. Data from preceding assessments (eg, cystoscopy) were not recorded. Data on severe side effects, such as oxygen toxicity and barotrauma to the ear, were retrospectively recoded at the end of the study. However, minor and well-known discomforts such as problems with equalization of the ear or oxygen-induced myopia were not assessed.

Assessment of patient perceived quality of recovery using EPIC

EPIC is a comprehensive, validated instrument developed to evaluate patient function and symptoms after prostate cancer

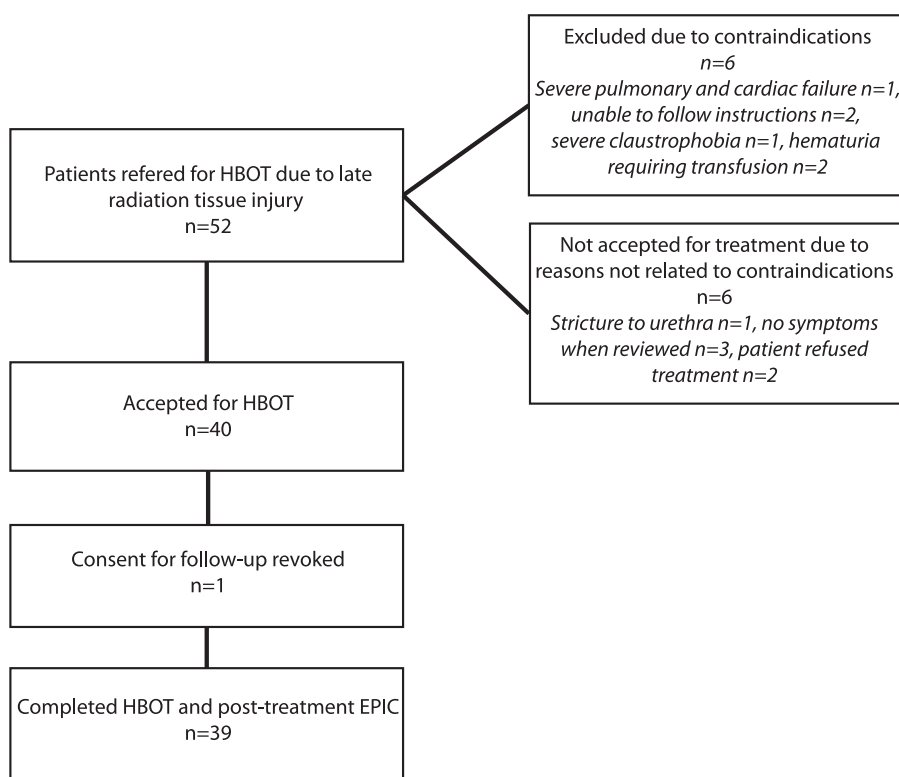


Fig. 1. Of 52 patients reviewed for inclusion, 40 patients were eligible. After 1 dropout, 39 patients were available for evaluation. EPIC = Expanded Prostate Index Composite; HBOT = hyperbaric oxygen treatment.

treatment. EPIC consists of 50 questions divided into 5 domains: bowel, urinary, sexual, hormonal, and psychological. There are 2 sections under each domain, the first for types of symptoms and the second for extent of suffering. The Likert scale format is used with scores from 0 to 100, where higher scores translate into better quality of life. This instrument has been validated for symptom scoring after radiation therapy for prostate cancer patients (12). The urology and bowel questions are, however, not specific to prostate cancer but cover symptoms shared by all groups of patients suffering from side effects after radiation therapy in the pelvic region. For homogeneity and because of a lack of other equivalent validated tools, patients were evaluated with EPIC regardless of the primary cancer diagnosis. We used only 2 of the subsets in EPIC: bowel and urinary domain.

Statistical analysis

A 1-way analysis of variance was performed on the EPIC score obtained before, during, and 6 to 12 months after HBOT; Tukey's post hoc test was used. The mean EPIC scores before and after treatment were compared for each specific subset of questions separately, within the urology and bowel domains, using paired parametric 2-tailed *t* test.

Results

Patient population

At baseline, 20 patients (51%) were affected in both their urinary and bowel function. On the basis of EPIC score and using a cutoff

of 80, 9 patients (23%) had symptoms of only the urinary tract and reported normal bowel function, and 7 patients (18%) had only symptoms from their bowel. The remaining 3 (8%) patients had EPIC score >80 in both domains.

Three patients received 29 and 1 patient received 28 treatments. The remaining patients completed the initial 30 treatments. Additional HBOT with 10 treatments was given to 22 patients. Mean number of treatments was 36 (range 28-40).

Effects of HBOT on cystitis

In the entire group of patients ($n=39$), EPIC scores in the urinary domain were significantly higher immediately after treatment (relative increase 22%, $P<.001$) and at 6- to 12-month follow-up (relative increase 21%, $P<.001$). When analyzing patients with a urinary EPIC score ≤ 80 ($n=29$), HBOT increased the EPIC score by 29% ($P<.001$) in the urinary domain, both early and 6 to 12 months after HBOT (Fig. 2). Individual responses to HBOT in the urologic domain are shown in Figure 4; 22 of the 29 patients (76%) with urinary EPIC score ≤ 80 before HBOT had an increase in EPIC score after treatment, leaving 7 patients (24%) as nonresponders to HBOT. Of the 29 patients with significant symptoms (urinary EPIC score ≤ 80), 9 (31%) had an EPIC score >80 at end of treatment and could therefore be said to have trivial symptoms.

Effects of HBOT on proctitis

For all patients ($n=39$), the EPIC score in the bowel domain was significantly higher directly after treatment (relative increase 24%,

Table 1 Patient demographics and cancer management

	Total
Number of patients	39
Age	71 (35-84)
Sex	
Male	35
Female	4
Tumor and treatment	
Prostate	34
External radiation (70-75 Gy)	23
Brachy therapy (28-33 Gy)	3
External radiation (50 Gy) and brachytherapy (20 Gy)	8
Radical prostatectomy	13
Rectal	3
External radiation 25 Gy	2
External radiation 50 Gy + chemotherapy	1
Rectal resection	3
Cervix	2
External radiation 60-64 Gy	2
Hysterectomy	1

$P < .001$) and at 6- to 12-month follow-up (relative increase 21%, $P < .001$). When analyzing patients with a bowel EPIC score ≤ 80 ($n = 27$), HBOT increased the EPIC score by 41% ($P < .001$) in the bowel domain early and by 39% ($P < .001$) 6 to 12 months after HBOT (Fig. 3). Individual responses in the bowel domain after HBOT are shown in Figure 4 where 24 of the 27 patients (89%) with significant symptoms before HBOT had an increase in EPIC score after treatment, leaving 3 patients (11%) as nonresponders to HBOT. Of the 27 patients with significant symptoms (bowel EPIC score ≤ 80), 6 patients (22%) had an EPIC score > 80 at end of treatment and could therefore be defined as having trivial symptoms.

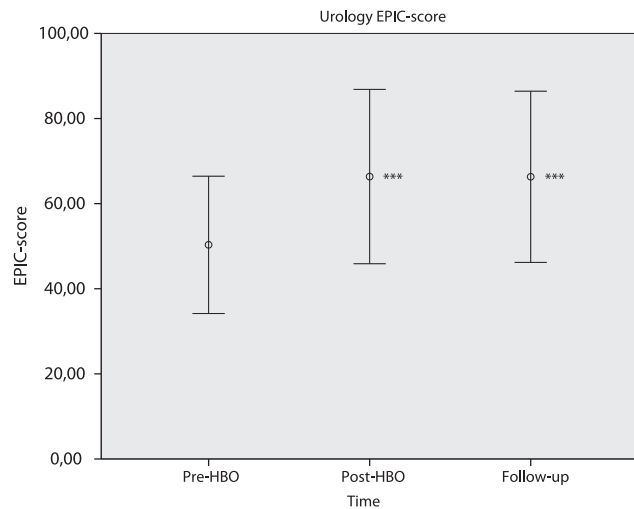


Fig. 2. Comparison of urology Expanded Prostate Index Composite (EPIC) score before, immediately after, and at 6 to 12 months after hyperbaric oxygen treatment (HBOT). Only patients with urology EPIC score ≤ 80 before HBOT are included. Mean and standard deviation are shown. A significant increase in EPIC score is seen after treatment. This increase remains significant compared with pre-HBOT values at follow-up. *** $P < .001$.

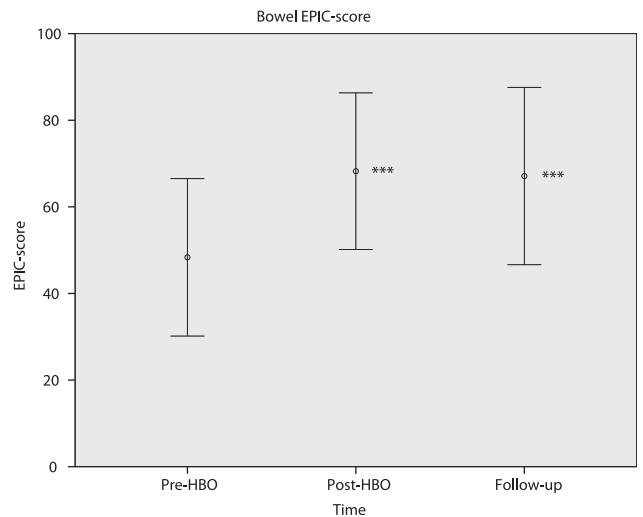


Fig. 3. Comparison of bowel Expanded Prostate Index Composite (EPIC) score before, immediately after, and at 6 to 12 months after hyperbaric oxygen treatment (HBOT). Only patients with bowel EPIC score ≤ 80 before HBOT are included. Mean and standard deviation are shown. A significant increase in EPIC score is seen after treatment. The increase remains significant compared to pre-HBOT values at follow-up. *** $P < .001$.

The mean EPIC score before and after HBOT for each symptom within the urology and bowel domains are shown in Table 2. The EPIC score of hematuria was not affected by HBOT in contrast to the increase of the EPIC score in all other symptoms within the urology domain. Within the bowel domain, all symptoms except stool consistency were significantly improved by HBOT (Table 2).

None of the patients experienced severe side effect from the treatment, such as oxygen toxicity with seizures or barotrauma to the ear.

Discussion

In the present study, patients with severe symptoms of late radiation-induced cystitis and proctitis were treated with HBOT. The main findings were that HBOT alleviated patient-perceived symptoms of radiation cystitis and proctitis, as demonstrated by a significant increase in EPIC score after treatment. No severe side effects were recorded. HBOT appears to be an effective and well-tolerated treatment modality for late radiation-induced soft tissue injuries in the pelvic region.

In patients with late radiation therapy-induced pelvic soft tissue injuries, objective findings vary and correlate poorly to patient-perceived symptoms. EPIC focuses on patient-perceived symptoms, but because it is highly sensitive, even mild symptoms will generate a reduction of the score. The level at which the symptoms can be considered significant for the patient's health is arbitrary. For the purpose of evaluation, we found it useful to establish such a level, enabling us to classify patients as significantly symptomatic or as having trivial symptoms. We set this level at an EPIC score of 80. Patients having a score of ≤ 80 were thus considered to have significant symptoms from that specific domain, and patients with a score > 80 were considered to have trivial symptoms.

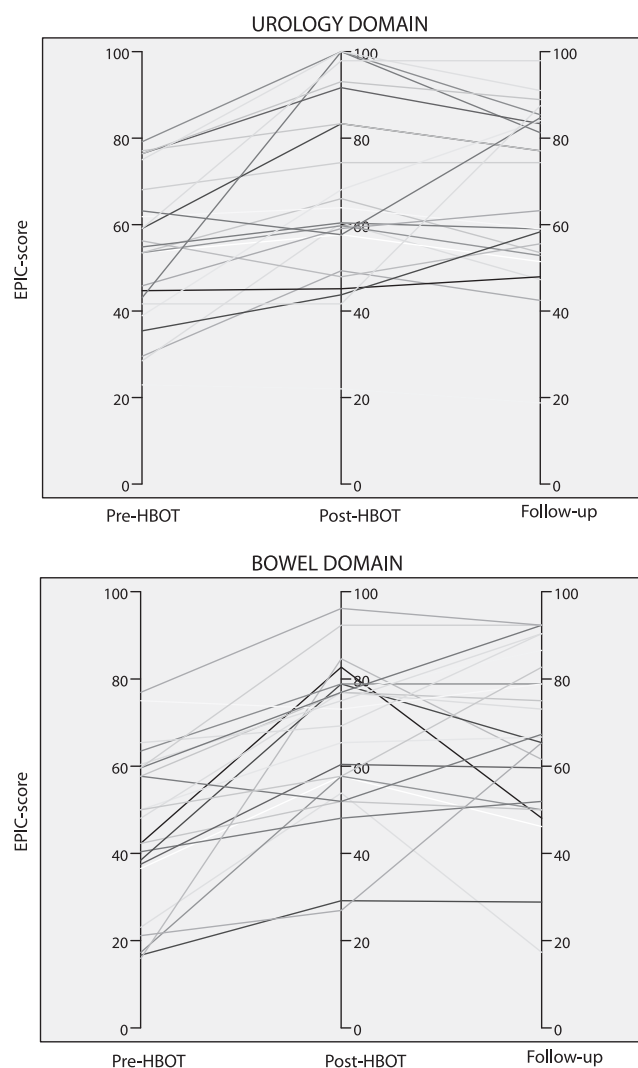


Fig. 4. Individual response to hyperbaric oxygen treatment (HBOT) in the urology and bowel domains for patients with an initial Expanded Prostate Index Composite (EPIC) score ≤ 80 pre-HBOT.

To our knowledge, only a few prospective and no randomized studies have been conducted on the effects of HBOT on late radiation-induced cystitis. Most of the previous studies have focused on hematuria, a late and severe symptom following radiation therapy that seems to respond well to HBOT. There are numerous retrospective studies on radiation-induced hemorrhagic cystitis showing resolution or marked improvement of hematuria after HBOT (6, 14-19). However, this patient group also has many other debilitating symptoms, such as urine leakage, painful micturition, frequent and/or imperative micturition, or pelvic pain. Findings on the effects of HBOT on these symptoms are limited.

In a retrospective study, Hampson et al reported positive effects of HBOT in radiation-induced cystitis ($n=44$), with 93% of the patients improved and 57% resolved, and for radiation-induced proctitis ($n=73$), 88% of the patients improved and 25% resolved (20). Treatment outcome was graded by the hyperbaric physician at the day of the last scheduled treatment, using a combination of objective data and patient interview. We report a similar response rate for radiation-induced proctitis. Our response rate for radiation-induced cystitis appears somewhat lower. We believe

Table 2 Change in Expanded Prostate Index Composite (EPIC) score pre- and post-hyperbaric oxygen treatment (HBOT)

	Mean EPIC score (SD)		<i>P</i> value
	Pre-HBOT	Post-HBOT	
Quantitative urinary questions			
Leakage of urine	37 \pm 42	52 \pm 45	.005
Hematuria	86 \pm 28	88 \pm 25	.72
Painful urination	72 \pm 36	84 \pm 31	.05
Bladder control	51 \pm 33	66 \pm 32	.007
Usage of diapers	53 \pm 48	70 \pm 39	.006
Urinary problems overall	17 \pm 20	43 \pm 33	<.001
Quantitative bowel questions			
Rectal urgency	35 \pm 39	64 \pm 40	.001
Leakage of stool	68 \pm 37	86 \pm 28	.002
Loose or liquid stool	53 \pm 26	58 \pm 25	.173
Bloody stools	56 \pm 34	75 \pm 31	.001
Painful bowel movements	67 \pm 33	80 \pm 25	.070
Bowel problems overall	19 \pm 23	49 \pm 28	<.001

Means and standard deviation before and directly after HBOT are shown together with significance for each domain.

this difference should be interpreted with caution because it is difficult to compare our study with that of Hampson et al for several reasons. First, we used a standardized and validated tool, EPIC, which reduces the risk of bias that can contribute to a more positive result. Second, compared with previous studies, hematuria was not as dominating a symptom in our study population because we had wide inclusion criteria for HBOT, while excluding patients with macroscopic hematuria requiring transfusions. Third, the mean number of treatments was higher in the study by Hampson et al, and it cannot be precluded that this may have contributed to a better outcome in their study. Thus, it is not unexpected that the effect of HBOT on hematuria in the present study may appear weaker than in the study of Hampson and coworkers. Our results do not by any means contradict the use of HBOT for hematuria but indicate that other distressful symptoms of late radiation-induced cystitis can also be effectively treated with HBOT.

The results for patients with proctitis are in line with a recent randomized double-blind controlled trial by Clarke et al showing that HBOT improved symptoms of proctitis compared with sham treatment, using the Subjective, Objective, Management and Analytic—Late Effects in Normal Tissues score (21). The same HBOT protocol as in the present study was used. In their study, the proportion of responders in the HBOT group was 89% compared with 63% in the sham group. In the present study, the proportion of patients with significant bowel symptoms decreased from 69% to 54% and the proportion of patients who had symptom improvement was 89%. There is evidence that late radiation tissue injury to the lower end of the bowel can be improved with HBOT (2). However, little has been reported concerning HBOT effect for late radiation-induced injury of other tissues in the pelvis.

HBOT is not widely accessible, and the treatment is given over a relatively long period of 6 to 8 weeks. In our study, none of the patients reported any serious complication as an effect of HBOT. Three patients received 29 and 1 patient received 28 treatments. These deviations from the protocol were all due to patient-related practical reasons. We consider this deviation from the prescribed 30 treatments minor and their treatments complete. This indicates that even if HBOT is a time-consuming treatment, it is well tolerated and accepted by patients.

The major limitation of the present study is the lack of a control group not receiving HBOT. Thus, one cannot exclude the possibility that some element in the improvement in symptoms from the urinary bladder and the bowel after HBOT was caused by spontaneous resolution of symptoms or a placebo effect. However, the fact that the result at follow-up (6-12 months) was unchanged compared with the result directly after HBOT makes a significant placebo effect less likely. If the reported improvement was in fact due to spontaneous resolution, the improvement might be expected to continue and increase at follow-up. To eliminate these confounders, a Scandinavian, prospective, randomized, controlled, multicenter trial, RICH-ART Radiation Induced Cystitis treated with Hyperbaric oxygen - A Randomized controlled Trial, has recently been initiated (www.clinicaltrials.gov; identifier: NCT 01659723). Cystoscopy was not routinely performed in all patients prior to HBOT referral, and cystoscopy findings are therefore not evaluated in our study. We do, however, believe that cystoscopy is indicated for these patients, and cystoscopy with biopsies is also included in the ongoing RICH-ART (Radiation Induced Cystitis treated with Hyperbaric oxygen - A Randomized controlled Trial) study. Another limitation of our study was that the patients were followed for only 6 to 12 months. A long-term follow-up with yearly evaluation up to 5 years is currently in progress. The strengths of this study include its prospective nature and relatively large patient population, as well as the assessment of effects of HBOT on both radiation-induced cystitis and proctitis, not only focusing on bleeding, and the use of a patient-perceived symptom scoring system, EPIC.

Conclusions

In this prospective cohort study, the effects of HBOT on patient-perceived symptoms of late radiation-induced cystitis and proctitis were assessed. In the majority of patients (>75%), HBOT alleviated symptoms, an improvement that was sustained for at least 6 to 12 months. Twenty to 30 percent of patients reported trivial symptoms after HBOT. Compliance with treatment was high, and side effects were few. We conclude that HBOT remains a promising treatment alternative for postradiation proctitis and cystitis even with symptoms other than bleeding and that these findings need to be confirmed in a larger randomized clinical trial setting.

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