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Patient-Reported Outcome Measures Following Hyperbaric Oxygen Therapy for Radiation Cystitis: Early Results From the Multicenter Registry for Hyperbaric Oxygen Therapy

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Study Need and Importance: A growing number of pelvic malignancy survivors who have undergone primary or secondary radiation therapy will develop radiation cystitis (RC), manifesting in recurrent, clinically significant hematuria and potentially debilitating lower urinary tract symptoms. Hyperbaric oxygen (HBO_2) therapy is the only noninvasive, severe RC treatment option associated with fewer bladder bleeding events; however, little is understood surrounding optimal HBO_2 timing, duration, and overall efficacy. The few published RC HBO_2 studies are limited by small sample sizes and limited reported data on patient-reported outcomes.

What We Found: In this study we compared prospectively collected Radiation Therapy Oncology Group Hematuria Scale, Urinary Distress Inventory Short Form, and EuroQol Five Dimension Five Level instrument from participants presenting with RC within a week before and after completing HBO_2 in the Multicenter Registry for Hyperbaric Oxygen Therapy Consortium. We found participants undergoing a median of 39 HBO_2 sessions reported improved hematuria (Figure), urinary function, and quality of life. Higher baseline hematuria scores, smoking, and nonprostate cancer history were associated with lower odds of hematuria improvement.

Limitations: This study was limited by the lack of a comparison control arm and a validated RC-specific patient-reported outcomes measure, as well as by a focus on short-term outcomes. Not all participants completed each of the 3 measures; however, demographic data between groups were similar. Further, the cohort primarily consisted of males with a prostate cancer history, which may limit generalizability to other RC cohorts.

Interpretation for Patient Care: This study demonstrates improved short-term patient-reported hematuria, urinary function, and quality of life in a large prospective cohort receiving HBO_2 for RC. Notably, individuals with higher baseline Radiation Therapy Oncology Group hematuria scores, a history of smoking, and treatment for nonprostate cancer had lower odds of hematuria improvement. These findings may be incorporated into RC treatment option shared decision-making.

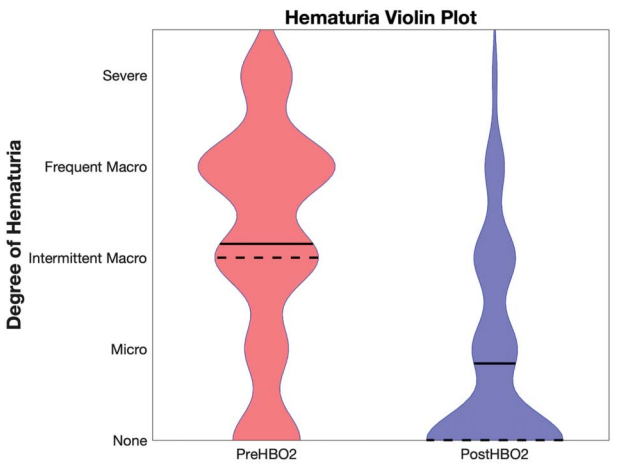

Figure. Mean (solid line) and median (dashed line) Radiation Therapy Oncology Group hematuria scores before vs after hyperbaric oxygen (HBO_2) therapy (n = 370). Sign test, $P < .001$.

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Patient-Reported Outcome Measures Following Hyperbaric Oxygen Therapy for Radiation Cystitis: Early Results From the Multicenter Registry for Hyperbaric Oxygen Therapy

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Purpose: Our purpose was to determine changes in patient-reported hematuria and urinary symptoms after hyperbaric oxygen (HBO_2) treatment for radiation cystitis (RC).

Materials and Methods: We analyzed prospectively collected data from the Multicenter Registry for Hyperbaric Oxygen Therapy Consortium accumulated within a week of beginning and ending HBO_2. Measures included the modified Radiation Therapy Oncology Group (RTOG) Hematuria Scale, Urinary Distress Inventory Short Form, and EuroQol Five Dimension Five Level instrument. RTOG hematuria and Urinary Distress Inventory Short Form scores were compared using the sign test. Logistic regression was used to evaluate characteristics associated with hematuria improvement.

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Author Contributions:

Conception and design: RAM, JCB.
Data analysis and interpretation: RAM, AEH, ERB, ZZ, JRR, WB, KS, LKW, JCB.
Drafting the manuscript: RAM, AEH, ERB, ZZ, JRR, WB, KS, LKW, JCB.
Critical revision of the manuscript for scientific and factual content: RAM, AEH.

Janet L. Peacock, MSc, PhD, Cstat, provided statistical and registry oversight at both Dartmouth and King's College London. Bolaji Coker manages the United Kingdom central registry at King's College London.

Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Results: A total of 470 registry patients had RC. The median age, number of HBO_2 sessions, and years after radiation were 73 (IQR 12) years, 39 (IQR 10) sessions, and 5 (IQR 8) years, respectively. Eighty-four percent of patients (393/470) had prostate cancer–related radiation. EuroQol Five Dimension Five Level scores improved from 0.83 (IQR 0.14) to 0.85 (IQR 0.22; $P < .001$. Three hundred seventy patients had complete RTOG hematuria scores that improved from 2 (IQR 2) to 0 (IQR 2; $P < .001$. Two hundred forty-six patients had complete Urinary Distress Inventory Short Form ratings that decreased from 33.3 (IQR 44) to 22.2 (IQR 33; $P < .001$). Regression analysis of those with visible hematuria before HBO_2 showed lower improvement odds associated with higher HBO_2 hematuria scores (odds ratio [OR] 0.44, 95% CI 0.26-0.73; $P < .01$), a smoking history (OR 0.44, 95% CI 0.21-0.92; $P = .03$), or a nonprostate cancer history (OR 0.32, 95% CI 0.10-0.99; $P = .05$).

Conclusions: HBO_2 for RC improved reported hematuria, urinary function, and quality of life. Higher baseline hematuria scores, smoking, and nonprostate cancer history were associated with lower odds of hematuria improvement.

Key Words: radiation injury, cystitis, hyperbaric oxygenation

THERE will be nearly 10 million pelvic malignancy survivors by 2026,[1] for whom radiation therapy remains a treatment mainstay. Notably, 10% or more of these survivors will develop chronic radiation cystitis (RC)[2,3] leading to increased health care utilization for lower urinary tract symptoms and bladder bleeding.[4] RC begins unpredictably with radiation-induced bladder mucosal injury promoting an inflammatory cytokine and angiogenic growth factor cascade leading to clinically significant bladder bleeding.[5] As cancer survivorship improves, the number of patients experiencing RC symptoms will inevitably increase. Existing definitive treatments for severe RC include caustic bladder irrigations,[6] bladder arterial embolization, and bladder removal with urinary diversion, which all carry high patient morbidity and mortality[7,8] Hyperbaric oxygen (HBO_2) therapy is the only noninvasive RC treatment option associated with fewer bladder bleeding events.[9-12]

HBO_2 treatment for RC is commonly performed by placing patients in pressurized chambers (140-250 KPa[13]) with 100% oxygen for 80 to 120 minutes per day for up to 40 to 60 consecutive sessions.[9] HBO_2 increases irradiated tissue oxygen levels intermittently, leading to increased angiogenesis and reduced inflammation.[14] The effects of different dosing treatment regimens remain unclear. While studies demonstrate HBO_2 leads to reduced hematuria,[11,12] most studies are limited by small sample sizes, insufficient power, and limited reported data on patient-reported outcomes (PROs).[10,15,16] To gather prospective data on HBO_2 efficacy across diverse conditions, including PROs for RC, the International Multicenter Registry for Hyperbaric Oxygen Therapy was established in 2011 under the registered identifier DERR1-10.2196/18857.[17] Today, this consortium, supported by the Undersea and Hyperbaric Medical Society, includes 26 centers regularly entering data.

The primary objective of this study was to evaluate short-term differences in pre- and post-RC HBO_2 treatment Radiation Therapy Oncology Group (RTOG) hematuria, Urogenital Distress Inventory (UDI) Short Form (UDI-6), and EuroQol Five Dimension Five Level instrument (EQ-5D-5L) PROs. The secondary objective was to assess whether there are patient characteristics associated with post-HBO_2 hematuria improvement. We hypothesized that hematuria and UDI scores improve following HBO_2 therapy and that there will be patient factors associated with hematuria improvement.

METHODS

Following Institutional Review Board approval from each participating site or via reliance on the Dartmouth Committee for the Protection of Human Subjects (IRB00024438), prospective, deidentified data from each of the 24 sites in the Multicenter Registry for Hyperbaric Oxygen Therapy Consortium that had treated RC patients were entered into a standardized REDCap template and uploaded to a central site.

Participants were included in the analysis if they carried a primary or secondary diagnosis of RC and had completed a minimum of 10 HBO_2 treatments.[18] To maximize hyperbaric site participation and promote effective, reliable, and consistent data collection, a limited number of key variables were selected as described previously.[15-17]

Outcome Measures

Baseline measures included demographics (age, race, ethnicity, sex, insurance, driving distance to HBO_2 center), reason for HBO_2 referral (eg, RC), and reason for radiation (eg, prostate, cervical, or other cancer), average radiation dose received, number of HBO_2 sessions, and HBO_2 pressure.

PROs

The RTOG hematuria scale has been used previously to measure HBO_2 outcomes[7,19-21] and includes 5 hematuria levels: 0 = none, 1 = microscopic, 2 = intermittent macroscopic, 3 = frequent macroscopic, 4 = severe hemorrhagic cystitis, and 5 = death from uncontrolled hematuria.

The UDI-6 was used to evaluate additional urinary symptoms and was adapted from the original long-form survey to improve efficiency and reduce patient burden.[22,23] It consists of 6 questions covering (1) urinary frequency, (2) urgency incontinence, (3) stress incontinence,

(4) stress incontinence severity, (5) obstructive urinary symptoms, and (6) lower abdominal, pelvic, and genital pain. Each question is graded on a Likert scale (0 = not at all, 1 = a little bit, 2 = moderately, and 3 = greatly). The average score of the 6 questions is multiplied by 33.3 and assigned a score between 0 and 100. Higher scores indicate more distress from urinary symptoms. A score of 33.3 or greater is associated with clinically significant urinary symptoms.[23] Patients with urinary catheters in place were included in the hematuria analysis but not the UDI analysis as they were only presented the UDI pain question.

The EQ-5D-5L[24] collects general health–related quality of life (QOL). It includes 5 questions covering mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and has been described previously.[17,25] Complications related to hyperbaric treatment were also recorded and included claustrophobia, barotrauma (otic, dental, or sinus), seizures, pneumothorax, and other measures as described previously.[17]

Statistical Analysis

Descriptive statistics were used to summarize demographic data including frequency and percent for categorical variables, and median and interquartile range for ordinal variables. The primary outcomes of interest taken within 1 week before and after HBO_2 (RTOG hematuria, UDI, and EQ-5D-5L scores) were compared using the sign test.

The secondary outcome of interest was post-HBO_2 hematuria improvement in a subset of patients reporting pre-HBO_2 baseline gross hematuria (RTOG hematuria score ≥ 2). This was analyzed by creating a binary variable, HBO_2 hematuria response where a hematuria responder was defined as someone who had a starting RTOG hematuria score ≥ 2 (macroscopic hematuria) and post-HBO_2 score ≤ 1 (microscopic or no hematuria). A nonresponder included those with a baseline RTOG hematuria score ≥ 2 and a post-HBO_2 RTOG hematuria score > 1. This is a useful clinical measure of response because it focuses on those patients who progress from visible blood to no visible blood. Patients with a baseline pre-HBO_2 score < 2 (eg, microscopic or no hematuria) were excluded from this subgroup analysis. Univariate analyses of factors associated with hematuria response were examined using χ^2 tests for categorical data (eg, smoking, diabetes, treatment pressure $>$ or $\leq$2.0) and 1-way Kruskal-Wallis ANOVA for continuous data such as age, number of HBO_2 treatments, and radiation dose. Multivariable analysis was conducted using logistic regression with hematuria response as the outcome variable and age, pretreatment RTOG score, radiation dose, diabetes, smoking, type of cancer (prostate yes/no), and treatment pressure low/high as predictors. Sex was not included in the logistic regression because it shared significant collinearity with prostate vs nonprostate cancer. Estimates were presented as odds ratios (ORs) and 95% CIs. All statistical analyses were performed in MATLAB version 2022a (Mathworks, Natick, Massachusetts).

RESULTS

Between 2012 and 2023, 470 patients undergoing RC HBO_2 treatment were entered into the registry. Of these, 370 had complete RTOG hematuria data and 246 had complete UDI-6 data. Table 1 lists the collected demographic variables, comorbidities, and reason for radiation. Patients were a median age of 73 (IQR 12) years, and 11% (51/470) were female. The main racial categories were 74% (347/470) White, 4.8% (23/470) Black, 3.1% Asian (15/470), and 16% (75/470) were missing a racial categorization. The cohorts missing PRO data had similar demographic characteristics to those with RTOG hematuria and UDI scores (Table 1). In this cohort, patients were referred for HBO_2 treatment 5 (IQR 8) years after a median of 68 (IQR 12) Gy of radiation exposure for primarily prostate cancer (n = 393 [84%]). Patients underwent 39 (IQR 10) HBO_2 sessions, at 2.0 atmospheres absolute (ata; 32%), 2.4 ata (63%), or 2.5 ata (4%).

Primary Outcomes

Post-HBO_2 PROs improved significantly for all measures: RTOG hematuria scores (2 pre- vs 0 posttherapy, $P < .001$; Figure 1), median UDI-6 scores (33.3 [IQR 44] before HBO_2 vs 22.5 [IQR 33] after HBO_2, $P < .001$; Figure 2), median EQ-5D-5L survey scores (0.82 [IQR 0.14] before vs 0.85 [IQR 0.21] after; $P < .001$), median EQ-5D-5L visual analogue scale scores (75 [IQR 25] before vs 80 [IQR 20] after; $P < .001$).

Secondary Outcomes

A total of 72% (268/370) of patients had a baseline RTOG hematuria score ≥ 2 and were included in the hematuria responder analysis, of whom 66% (177/268) demonstrated a positive response. Univariate analysis (Table 2) of patient factors demonstrated a higher proportion of participants having nonprostate cancer radiation (21% in nonresponder vs 9% in responder, $P < .01$) and HBO_2 RTOG hematuria score > 2 (78% in nonresponder vs 58% responder, $P < .001$) in the nonresponder group. Logistic regression analysis (Table 3) showed significant associations for baseline RTOG hematuria score, which had lower odds of hematuria response (OR 0.44, 95% CI 0.26-0.73; $P < .01$), as did smoking history (OR 0.44, 95% CI 0.21-0.90; $P = .03$) and a history of nonprostate cancer (OR 0.32, 95% CI 0.01-0.99; $P = .05$).

The most common treatment complication was otic barotrauma (9%, n = 42) requiring bilateral (n = 19), unilateral ear tubes (n = 5), or myringotomies (n = 3). Fifteen (3.1%) patients reported claustrophobia, 1 stopped treatment, 2 missed treatment(s), and 12 managed claustrophobia without HBO_2 treatment disruption. Four patients (0.85%) developed a seizure. Of those, 2 completed HBO_2, 1 was treated at a reduced pressure, and 1 stopped due to multiple seizures.

Table 1. *Patient Demographics*

	Overall cohort (N = 470)	RTOG hematuria cohort (n = 370)	UDI-6 cohort (n = 246)	Non-RTOG hematuria cohort (n = 100)	Non–UDI-6 cohort (n = 224)
Age, median (IQR), y	73 (12)	73 (13)	73 (13)	74 (11)	74 (11)
Female, No. (%)	51 (11)	39 (11)	30 (12)	12 (12)	21 (9.4)
Race, No. (%)					
White	347 (74)	278 (75)	187 (76)	69 (69)	160 (71)
Black	23 (4.9)	20 (5.4)	9 (3.6)	3 (3.0)	14 (6.3)
Asian	15 (3.2)	14 (3.7)	11 (4.4)	1 (1.0)	4 (1.8)
Missing	75 (16)	49 (13)	31 (13)	26 (26)	44 (20)
Comorbidity, No. (%)					
Diabetes	115 (24)	91 (24)	52 (21)	24 (24)	63 (28)
Current or former smoking	155 (33)	119 (32)	81 (33)	36 (36)	74 (33)
Reason for radiation, No. (%)[a]					
Prostate cancer	393 (84)	312 (85)	202 (82)	81 (81)	191 (85)
Cervical cancer	20 (4.3)	16 (4.3)	11 (4.5)	4 (4.0)	9 (4.0)
Other (colorectal, sarcoma, bone, breast)	54 (11)	40 (11)	33 (13)	14 (14)	21 (9.4)
Time from radiation exposure to HBO_2 referral, median (IQR), y	5 (8)	5 (8)	4 (7)	5 (8)	6 (8)
Radiation dose, median (IQR), Gy	68 (12)	68 (12)	68 (14)	66 (20)	68 (16)
HBO_2 treatments, median (IQR)	39 (10)	39 (10)	39 (10)	40 (10)	39 (10)
Prescribed HBO_2 dose ata, No. (%)[a]					
2.0	151 (32)	112 (30)	60 (24)	39 (39)	91 (41)
2.4	297 (63)	240 (65)	174 (71)	57 (57)	123 (55)
2.5	19 (4.0)	17 (4.7)	11 (4.5)	2 (2.0)	8 (3.5)
Missing	3 (0.64)	1 (0.27)	1 (0.41)	2 (2.0)	2 (0.89)

Abbreviations: ata, atmospheres absolute; HBO_2, hyperbaric oxygen; RTOG, Radiation Therapy Oncology Group; UDI-6, Urogenital Distress Inventory Short Form.
[a] Due to 2 significant digit specification, total cohort percent may not add up to 100.

DISCUSSION

RC patients undergoing a median number of 36 HBO_2 sessions reported significant short-term improvement in RTOG hematuria scores, UDI scores, and QOL. Higher pre-HBO_2 RTOG hematuria scores (>2), a history of smoking, and treatment for nonprostate cancer were associated with lower odds of improvement in short-term post-HBO_2 RTOG hematuria. This study supports the efficacy and safety of HBO_2 for managing RC and highlights the need for further data collection to determine the optimal treatment protocol, treatment duration, and

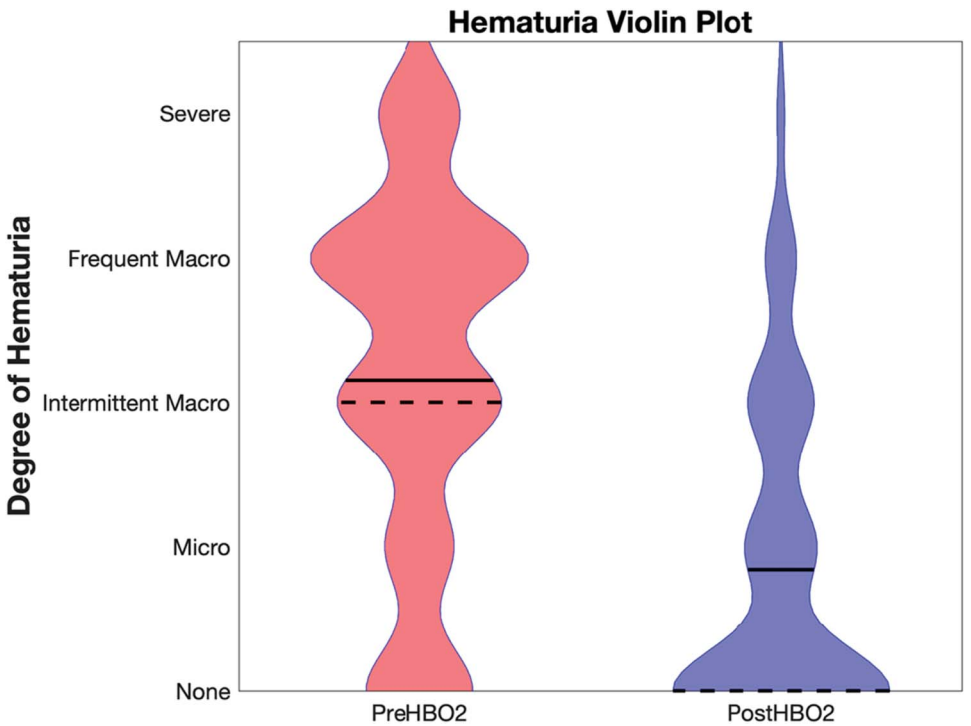

Figure 1. Mean (solid line) and median (dashed line) Radiation Therapy Oncology Group hematuria scores before vs after hyperbaric oxygen (HBO_2) therapy. Sign test, $P < .001$.

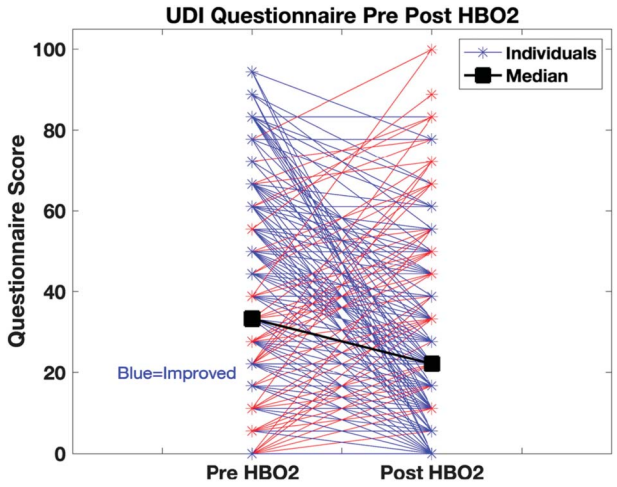

Figure 2. Urogenital Distress Inventory (UDI)–6 scores before vs after hyperbaric oxygen (HBO_2) therapy. Sign test, $P < .001$.

patient selection factors for this minimally invasive intervention.[26]

Prior work evaluating HBO_2 has focused on outcomes such as reducing blood transfusion rates or avoiding the need for cystectomy and urinary diversion.[7,27,28] Recent studies include the importance of patient perceived impact on urinary function. In a recent randomized controlled trial, 41 patients receiving HBO_2 had significantly greater improvement in mean (SD) Expanded Prostate Index Composite: 18 (18) points vs 7.7 (15) points in the 38 participants undergoing usual care.[16] Their analysis excluded more severe cases of RC including those requiring blood transfusion in the prior 4 weeks, indwelling Foley catheters, and a history of prior failed HBO_2 treatment. Further, although the Expanded Prostate Index Composite is validated to measure some urinary and sexual health components following interventions for prostate cancer, it does not include RC-specific symptoms such as gross hematuria or pelvic pain.[19,20,29]

Table 2. *Univariate Hematuria Response (n = 268)*

Patient factor	Nonresponder (n = 91)	Responder[a] (n = 177)	P value
Age, median (IQR), y	73 (12)	74 (12)	.57
Female, No. (%)	11 (12)	10 (5.6)	.06
Radiation dose, median (IQR)	66 (10)	70 (11)	.08
Baseline RTOG hematuria score >2	71 (78)	102 (58)	< .01
HBO_2 therapy sessions, median (IQR)	31 (11)	39 (10)	.31
Nonprostate cancer, No. (%)	19 (21)	16 (9.0)	< .01
Diabetic, No. (%)	43 (47)	24 (14)	.71
Smoker, No. (%)	38 (42)	54 (31)	.06
ata >2, No. (%)	67 (74)	118 (67)	.27

Abbreviations: ata, atmospheres absolute; HBO_2, hyperbaric oxygen; RTOG, Radiation Therapy Oncology Group.
χ^2 for categorical and 1-way Kruskal-Wallis ANOVA for continuous variables.
[a] Hematuria response was defined as someone who had a starting RTOG hematuria score $\geq$ 2 (macroscopic hematuria) and post-HBO_2 score $\leq$ 1 (microscopic or no hematuria).

The UDI has been used to evaluate the impact of pelvic malignancy treatment, including radiation, on urinary function. Erekson et al performed a cross-sectional analysis of women undergoing endometrial cancer treatment, where 36% of the cohort required radiation. Mean (SD) UDI scores were significantly worse for participants with a prior history of radiation compared to those without: 47 (27) vs 36 (22).[15] In contrast to our study including primarily patients with prostate cancer–related pelvic radiation disease, the Erekson cohort median baseline UDI scores were lower. Although the UDI has not been specifically validated to measure the impact of pelvic radiation, the findings support the potential for worse RC urinary symptom development in nonprostate cancer radiation treatment.[5-9]

We found overall improvement in EQ-5D-5L scores, which suggests HBO_2 RC symptom treatment may improve overall QOL. This has been demonstrated in other studies using health-related QOL measures to evaluate HBO_2 impact.[16] The small change overall is likely related to the large variability in responses and cystitis severity within the cohort. The reasons for this variability will require further study.

The current study demonstrated significant improvement in reported RTOG hematuria scores following HBO_2, consistent with results of prior studies.[9,20] In a recent scoping review, 75% of RC patients improved by 1 RTOG hematuria grade. This is supported by our findings, where the median pre-HBO_2 hematuria score improved from 2 to 0. In the analysis examining those with a clinical response defined by going from an RTOG score $\geq$ 2 to an RTOG score of 1 or less (ie, from visible to no visible hematuria) higher baseline RTOG score, treatment for nonprostate cancer and being a current/former smoker was associated with lower odds of a clinical hematuria response. Liss et al also found significantly more improvement in RTOG hematuria score and lower risk of bleeding recurrence in those with lower levels of bleeding at the time of HBO_2 initiation.[20] This was also demonstrated by Mougin et al,[10] where patients presenting with an RTOG hematuria grade < 3 were more likely to have a successful outcome.

In addition to higher risk of HBO_2 failure, as similarly demonstrated in HBO_2 use for nonhealing wounds,[30] smoking history may indicate collinearity between nonprostate cancer pelvic malignancy with greater prevalence of smoking such as bladder[31] cancer, which would carry an inherently higher risk of gross hematuria. These results also highlight the importance of counseling patients with a history of smoking on potentially worse HBO_2 outcomes. We recommend patients with RC undergoing HBO_2 receive smoking cessation counseling.

This cohort highlights variation in RC HBO_2 referral patterns. While a portion of the cohort had

Table 3. *Logistic Regression Analysis: Factors Associated With Hematuria Response*

Patient characteristic	OR	95% Lower CI	95% Upper CI	P value
Age	1.00	0.97	1.04	.83
Nonprostate cancer	0.32	0.10	0.99	**.05**
Diabetes	1.33	0.56	3.15	.52
Smoking	0.44	0.21	0.90	**.02**
Radiation dose	1.01	0.99	1.03	.57
Baseline RTOG hematuria score	0.44	0.26	0.73	**< .001**
Total HBO_2 sessions	1.02	0.98	1.05	.36
ata >2.0	1.06	0.47	2.38	.89

Abbreviations: ata, atmospheres absolute; HBO_2, hyperbaric oxygen; OR, odds ratio; RTOG, Radiation Therapy Oncology Score.
Bolded values indicate $P \leq .05$
[a]Hematuria response was defined as someone who had a starting RTOG hematuria score ≥ 2 (macroscopic hematuria) and post-HBO_2 score ≤ 1 (microscopic or no hematuria).

severe RTOG hematuria scores, a subset did not have gross hematuria at the start of HBO_2. This is exemplified by the median presenting RTOG hematuria score of 2 (intermittent macroscopic hematuria) and UDI median score of 33, suggesting some patients undergo HBO_2 for less severe or possibly intermittent symptoms. The intermittency of[5-9] RC symptoms could also influence the results because the start of HBO_2 may not always coincide with times patients experience their most severe and debilitating RC symptoms. Currently, no consensus exists on the best time to initiate HBO_2 treatment, and evidence-based guidelines are needed.

Complications related to HBO_2 were rare (Table 4). Like other series, the most common side effect was otic barotrauma.[28,29] A minority required operative intervention for this with either pressure-equalizing tubes or myringotomy. The most serious side effect was seizure in 4 patients; however, only 1 had to stop treatment.

While we present one of the largest series of prospectively collected PROs data following HBO_2, the data have limitations. This study lacks a control arm as it uses data from an HBO_2-focused registry. Also, not all participants completed all 3 measures before and after HBO_2, though the demographics of the cohorts with and without PROs were similar. Furthermore, although prior studies used the UDI to measure urine-related QOL in patients with pelvic radiation disease, it has not been validated in an RC population. We chose this short-form option because it included key RC complaints including urinary urgency, pain, and incontinence. Generalizability may be affected by the cohort primarily consisting of males with a prostate cancer history. This may have limited our analysis of factors related to hematuria and UDI improvement following HBO_2. Finally, this analysis only focuses on short-term HBO_2 outcomes; future directions will include longer-term follow-up. Continuing and expanding this work will not only increase follow-up duration, but also lay the groundwork for future RC-specific PRO development.

Table 4. *Reported Hyperbaric Oxygen Complications (N = 470)*

HBO_2 complication	No. (%)
Ear barotrauma	42 (8.9)
Claustrophobia	15 (3.1)
Seizure	4 (0.85)

Abbreviations: HBO_2, hyperbaric oxygen.

CONCLUSIONS

In summary, our study demonstrates improved short-term patient-reported hematuria, urinary function, and QOL in a large prospective cohort receiving HBO_2 for RC. Notably, individuals with higher baseline RTOG hematuria scores, a history of smoking, and treatment for nonprostate cancer had lower odds of hematuria improvement. These findings may be incorporated into RC treatment option shared decision-making. Ongoing investigations aim to delve deeper into these observations, elucidate the optimal timing for initiation, determine the optimal treatment duration, and define the most suitable patient demographic within the spectrum of RC.

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EDITORIAL COMMENT

Radiation cystitis (RC), a rare but severely debilitating bladder condition that may affect patients after pelvic radiation, has significant unmet medical needs. To date, the number of cancer survivors in the US is estimated to be 18 million, and this number is expected to exceed 20 million by 2026.[1] The effects of radiation-induced cystitis can occur as early as 6 months to as late as 20 years after radiation treatment.[2] Although no definitive treatment is currently available, various interventions are employed to manage the symptoms of RC. One such treatment that has shown positive outcomes is hyperbaric oxygen (HBO_2) therapy.

Moses et al present one of the largest multi-institutional studies using prospectively collected, paired pre- and post-patient–reported hematuria and urinary outcomes for those undergoing HBO_2 therapy for RC.[3] The study should be commended for its large sample size, diverse patient characteristics, and utilization of an objective outcome measure. Overall, 66% of patients with available RTOG (Radiation Therapy Oncology Group) hematuria scores had an RTOG hematuria score < 1 at 1 week post completion of HBO_2 therapy and were considered treatment responders. The authors provide initial insight into factors determining the chance of responding to HBO_2 therapy. Of the 470 patients enrolled in the study, 85% were prostate cancer survivors, which is not surprising given the high prevalence of prostate cancer. However, the authors identified nonprostate cancer survivors as being at increased risk for not responding to HBO_2 therapy. Several potential factors may warrant further investigation when evaluating the different trends between responders and nonresponders. Are women at increased risk due to hormonal differences? Does the size of the irradiated area, rather than the dose, negatively impact the success of HBO_2 therapy? If a current or past smoker has a lower chance of HBO_2 therapy response, is there a correlation with the duration of smoking, and can quitting smoking before radiation therapy or before HBO_2 therapy offer any chance of improved outcome? Does the type or length of diabetes diagnosis impact HBO_2 treatment response? And if a patient is a nonresponder, would adding HBO_2 sessions increase the chance of treatment success?

In addition to improving hematuria, this study demonstrates an overall decrease in urinary symptoms after HBO_2 therapy.[3] To assess urinary symptoms, the authors use the UDI-6 (Urinary Distress Inventory Short Form) questionnaire, which is a validated survey used to assess symptom distress for women suffering from urinary incontinence.[4] As noted by the authors, no validated questionnaire to assess urinary symptoms in patients with RC has been developed. Still, the UDI-6 seems appropriate as it covers the symptoms observed in RC patients. While the primary intent of HBO_2 therapy is to address hematuria, it is also encouraging to observe patient-reported improvements in urinary symptoms. This may be attributed to the increased proliferation of stem cells that may subsequently aid in regenerating bladder tissue and bladder function.[5] If so, one may expect further symptom improvement after HBO_2 therapy completion. While some patients had significant improvement of urinary symptoms, not all seemed to fare well. The extent to which those with improved hematuria also have improved urinary symptoms is of interest.

However, the findings should be interpreted with some caution due to limitations in data collection, potential selection bias, and the absence of a control group. The data were collected within 1 week of the last hyperbaric visit, and therefore the data represent only immediate treatment effects. Additionally, there were no specific HBO_2 delivery protocol requirements for the participating sites, and the study was not large enough to see differences in site HBO_2 protocols. Even though these are current study limitations, we applaud the authors and the Multicenter Registry for Hyperbaric Oxygen Therapy Consortium members for forming a research group to answer these questions and many more in the future. It is essential we develop research consortiums like this one to help better understand the use of HBO_2 in RC patients, and we are hopeful that long-term follow-up of this patient population will provide further insight into the future of HBO_2 therapy for patients suffering from the consequences of radiation therapy.

The number of cancer survivors living in the US continues to increase each year due to the growth and aging of the population and because of improvements in treatment and earlier diagnosis of cancer. As the population of cancer survivors in the US continues to grow and becomes more diverse, it is important we meet the needs of our cancer survivors.

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REPLY BY AUTHORS

We thank the authors of this insightful editorial, which encapsulates the key findings, limitations, and potential future directions of this work.[1] Although a challenging and unpredictable disease process to study and treat, radiation cystitis will no doubt lead to major morbidity and reduce quality of life for a growing number of pelvic cancer survivors. As such, efforts to study optimum management strategies must continue. Despite the inherent limitations of a large, observational cohort study, we found overall improvement in patient-reported hematuria, urinary function, and quality of life.[1] With continued registry recruitment and longer-term follow-up, we will use the Multicenter Registry for Hyperbaric Oxygen Therapy Consortium to better elucidate long-term hyperbaric oxygen efficacy, optimum initiation timing, and treatment duration for radiation cystitis management.

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