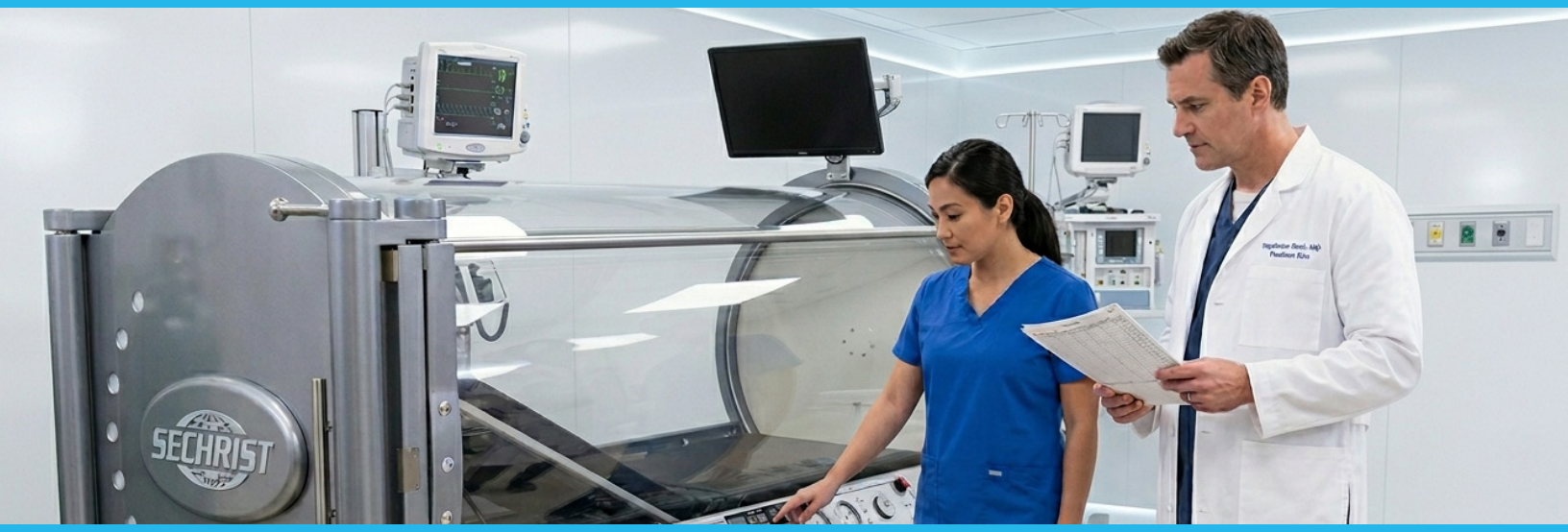
The Use of Hyperbaric Oxygen Therapy for Radiation Cystitis



Introduction

As part of a People-first, Patient-centered organization, Healogics® is dedicated to continuously improving patient outcomes. In support of our mission to FIND. TREAT. HEAL.™ Healogics Medical Affairs continually reviews studies and literature to find ways to improve access to and the delivery of exceptional care to the patients whom we serve. In this white paper, we will review the use of hyperbaric oxygen therapy (HBOT) as a treatment modality for patients with Radiation Cystitis. The topic was discussed briefly in the white paper entitled, "The Use of Modalities in Wound Care Part 2: Hyperbaric Oxygen Therapy (An update on HBOT Therapy coverage, NCD implications)". This current white paper will provide updated recommendations based on a review of more recent literature and make a recommendation to consider the earlier use of HBOT for patients with delayed radiation cystitis.

Understanding the Problem

It is estimated that there are 714,000 cases of pelvic malignancy each year in the United States.[1] Radiation therapy is used in up to 50% of all patients being treated for cancer.[2] As radiation techniques have improved over time, with more precise localization, the hope was that the incidence of radiation injuries would be reduced. The literature has not yet supported any reduction with some showing no changes at all between older techniques and current approaches.[3,4] One author reviewed 1,198 consecutive urological hospital admissions at a tertiary care facility.[5] In total, 23% of all admissions were secondary to radiation therapy complications. Another author reviewed 709 patients with RC and found that the average patient required 2.5 admissions with a length of stay of 7.6 days and 52% of them required a blood transfusion.[6]

Of the approved indications for HBOT, delayed radiation tissue injury is one of the most commonly listed indications for patients being treated with HBOT. In fact, a recent review of billing records from CMS found that delayed radiation tissue injury accounted for 40% of all HBOT billings.[7] This was consistent with informal surveys of HBOT centers in the United States, where nearly one half of patients had radiation injury as the indication

for HBOT. The International Multicenter Registry for Hyperbaric Oxygen Therapy published results in 2022 that noted the most common indication for HBOT was delayed radiation injury accounting for 32.1% of the cases.[8] Radiation injuries account for 34% of all HBOT cases at Healogics managed centers.

Within delayed radiation injuries, radiation cystitis is a common diagnosis for which HBOT can provide significant benefits when used as a component of a comprehensive treatment plan. Radiation cystitis is a complication from pelvic radiation used to treat a variety of pelvic tumors, including prostate, bladder, cervical, endometrial, and anorectal. Hemorrhagic radiation cystitis, a subset of radiation cystitis , is a more severe form of radiation cystitis and the condition most commonly treated with HBOT. Radiation cystitis affects both men and women, with men more commonly affected with a ratio of 2.8:1.[9] Radiation cystitis can occur as an acute injury, either during or within 6 months of treatment, or as a chronic condition that manifests 6 months to many years post radiation therapy.[9] Symptoms of radiation cystitis can range from mild symptoms including increased frequency, urgency, and dysuria to more significant urinary incontinence, decreased bladder capacity, hematuria, bladder fistula formation, or bladder necrosis.[10] One published review found that radiation cystitis occurs in 23-80% of patients who receive pelvic radiation, with 5-10% of patients developing chronic hemorrhagic cystitis .9 Hemorrhagic cystitis generally occurs in patients who receive radiation doses of 45-55 Gy, with a significant increased risk at cumulative doses greater than 60 Gy.[11]

Treatment for radiation cystitis depends on the acuity of the disease process. When significant hematuria is present, the patient requires hospitalization with initial treatment consisting of fluid resuscitation, continuous bladder irrigation, and cystoscopy with clot evacuation and possible fulguration. Additional therapy with oral medications, intravesical treatments, and HBOT can be considered if the patient is stable but continues to have persistent symptoms. A review of the management strategies of hemorrhagic cystitis from 2023 states that “currently no standard-of-care exists for patients with HC and existing treatments may be ineffective, risky, or both”.[12]

The following sections of this white paper will discuss currently available therapies for radiation cystitis and hemorrhagic cystitis, limitations, risks, and both short- and long-term outcomes. A brief review of the literature will be presented along with a recommendation for initiating HBOT earlier in the life cycle of the disease.

Treatment Options

Oral therapy includes sodium pentosan polysulfate (SPP), aminocaproic acid, and estrogen. SPP, is thought to repair the lining of the bladder, and is beneficial in treating hemorrhagic cystitis but is associated with side effects, including liver dysfunction and maculopathy, leading to the United States Federal Drug Administration (FDA) to issue a formal warning for patients using it long term.[10] Oral aminocaproic acid, which prevents fibrin degradation and clot breakdown, was used historically, but there has been concern for hepatic and renal injury, risk of deep vein thrombosis/ pulmonary embolism, and muscular damage.[13] Given these risk factors, its use has fallen out of favor. Estrogen, thought to affect the vascular intimal lining and strengthen the vessels. has been evaluated in several small studies for hemorrhagic cystitis with short-term success in hematuria cessation, but has not been evaluated for long-term results.[14-16] It would be important to discuss the primary tumor prior to using estrogen to ensure the original tumor was not hormone sensitive.

Intravesical therapy involves the instillation of medications directly into the bladder in order to treat the mucosal lining. Intravesical therapies include alum, silver nitrate, aminocaproic acid, and formalin. These agents have varying degrees of short-term success, but studies that have looked at long-term results generally report limited success, with high recurrence rates of

hematuria. In addition, some of these agents can lead to further scarring and damage of the bladder mucosa, making symptoms even worse.

In refractory hemorrhagic cystitis, treatment options include vesical artery embolization to control the bleeding or cystectomy and diversion (removal of the bladder with the creation of a urinary ostomy on the abdominal wall). Vesical artery embolization is generally reserved for patients who are not good candidates for operative intervention and carries a risk of bladder necrosis. Several studies have shown significant morbidity and mortality of cystectomy for radiation cystitis. One study showed severe complications in 42% of cases, with a 90-day mortality of 16% and a case series reported a mortality rate of 44%.[17,18]

HBOT Treatment for Radiation Cystitis

Historically, there are limited therapeutic options to achieve long-term resolution of radiation cystitis. Based on the literature, HBOT is an important treatment option for radiation cystitis. The Hyperbaric Medicine Indication Manual, 15th Ed., published by the Undersea and Hyperbaric Medical Society (UHMS), discusses treatment of radiation cystitis with 100% oxygen at 2.0-2.4 ATA for 80-90 minutes for 40 sessions, with an additional 20 sessions if needed, for up to 60 total dives to achieve a durable resolution of symptoms. HBOT has traditionally been considered a second- or third-tier option in the treatment algorithms. There has been recent literature, however, supporting both short-term and long-term success of HBOT for hemorrhagic cystitis specifically, as well as radiation cystitis more broadly. [7]

The traditional understanding of the mechanism by which delayed radiation affects soft tissue was centered around hypoxia caused by the process of obliterative endarteritis. There is growing research, however, to support an additional hypothesis, known as the fibro-atrophic effect, in which radiation-induced apoptosis, stem cell depletion and subsequent fibrosis result in delayed radiation soft tissue damage.[19] The fibrosis itself may lead to tissue hypoxia by “squeezing out” the small vessels in the tissue. There is likely a combination of both vascular damage and fibrosis caused directly by the radiation therapy that leads to the clinical symptoms seen in radiation cystitis.

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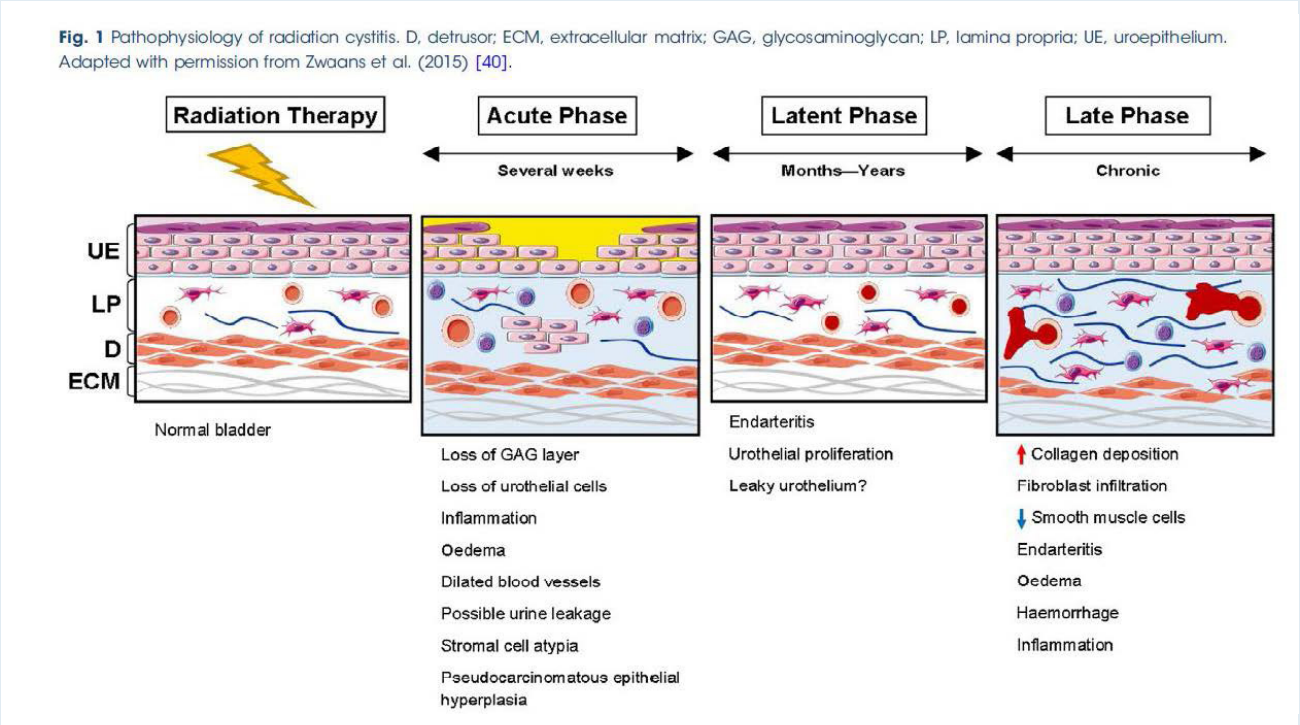


Fig. 1 Pathophysiology of radiation cystitis. D, detrusor; ECM, extracellular matrix; GAG, glycosaminoglycan; LP, lamina propria; UE, uroepithelium. Adapted with permission from Zwaans et al. (2015) [40].

As discussed in the Hyperbaric Medicine Indications Manual, 15th Ed ,the effects of HBOT on radiation-damaged tissue are thought to involve three mechanisms of action. To begin, angiogenesis is induced by HBOT, leading to improved tissue oxygenation. The increased perfusion results in decreased tissue fibrosis. Finally stem cells are stimulated to mobilize, home to the damaged tissue, and subsequently differentiate. Therefore, HBOT is unique as a treatment modality due to the fact that it can directly treat, and potentially reverse, the effects of radiation injury to the soft tissue.[7]

In earlier reviews, much of the literature on the use of HBOT for hemorrhagic cystitis or radiation cystitis consisted of small case studies. The majority of these studies, while limited in size, demonstrated positive benefits.[20] Several updated meta-analyses of current literature have been done in an attempt to collate a larger number of patients. In 2020, Villiers, et al., assessed the effect of HBOT on radiation cystitis via a meta-analysis of 20 studies which included 815 patients.[11] The authors found that some improvement in cystitis-related symptoms were observed in 64.8-100% of patients, with a weighted average of 87.3%. The majority of the patients, with a weighted average of 65.3%, were free of symptoms after HBOT. Yang et al. in 2024, reported a meta-analysis of 14 studies, including 556 patients, to determine the effect of HBOT for the treatment of hemorrhagic radiation cystitis.[21] These authors found that in 54.9% of patients with hemorrhagic cystitis, there was complete remission with an additional 35.1% experiencing partial remission. Complete remission was defined as the disappearance of all symptoms, while partial remission included patients with a reduction of the frequency or severity of macroscopic hematuria, or an improvement in a patient-reported outcomes measure as identified a standardized scoring metric.

More recently, a randomized controlled trial, the RICH-ART trial, evaluated the use of HBOT in treating radiation cystitis and has reported on both short and long-term results.[22] The study randomized 87 adult patients with previous pelvic radiotherapy and who were referred to an HBOT center for radiation cystitis and were randomized to either HBOT or standard of care. The HBOT therapy consisted of 30-40 sessions with 100% oxygen at 2.4 ATA (240-250 kPa) for 80-90 minutes. Patients were excluded if they had any prior hyperbaric oxygen therapy. The primary short-term outcome was an improvement in patient-reported urinary symptoms at 6-8 months using the Expanded Prostate Cancer Index Composite (EPIC) urinary questionnaire. This validated scoring system is used in the Urological literature and is accepted as a valid outcome metric. The EPIC score evaluates 4 key domains, urinary, bowel, sexual and hormonal. The questions use a Likert scale and the values range from 0-100 with higher numbers indicating improved quality of life. The study identified that, in order for improvement to be clinically significant, an improvement of greater than or equal to 9.0 was required. The patients randomized to HBOT demonstrated a 17.8 increase in their score compared to a 7.7 score improvement for the standard of care arm. When analyzing the results using the 9.0 cut off, 73% of patients in the HBOT had significant quality of life improvement, compared to 34% for the control arm. A five-year follow-up from this study was recently published in May, 2025.[23] After completion of the initial randomized control trial, all patients within the standard of care group were offered HBOT as a cross-over trial design. The outcome measured in this new report included the change in EPIC score from before HBOT treatment to 5 years post-HBOT treatment. Just over half of the patients included in the initial study were available for assessment at 5 years. At 6 months after HBOT, the average score improvement was 18.0 points, which remained stable at 19.1 points at 5 years. This 5-year follow-up demonstrates the sustained response to HBOT for radiation cystitis, in contrast to other treatment options, where long-term results are generally not reported or are poor.

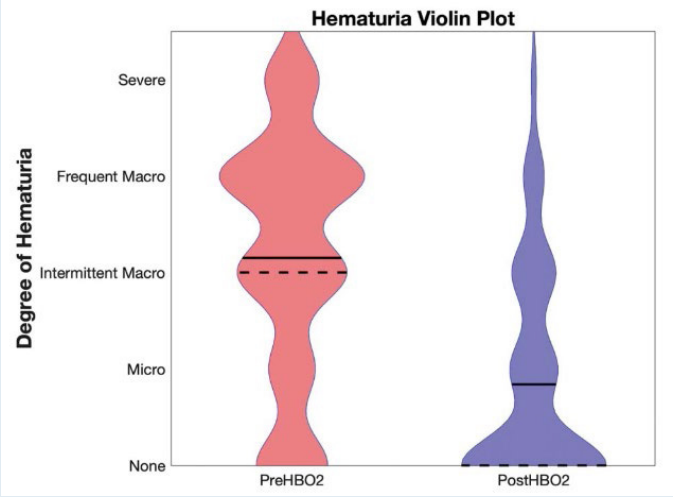
Another recently published study evaluated outcomes in both subjective clinical findings and patient-reported outcomes was from the

Multicenter Registry for Hyperbaric Oxygen Therapy Consortium.[24] The paper reported the early results of 470 patients with radiation cystitis. Hematuria scores based on the Radiation Therapy Oncology Group scoring system improved significantly after HBOT, Fig 1. Patient-reported outcomes using the Urinary Distress Inventory Short Form were also clinically significantly improved after completion of HBOT. An additional standard quality of life survey, not specific to radiation cystitis, was performed and demonstrated an overall improved quality of life after treatment.

As with any of the treatments discussed, some patients are not responsive to HBOT. Multiple studies have looked into risk factors that are associated with decreased effectiveness of HBOT in certain patients. Risk factors identified include higher radiation doses, shorter interval between completion of radiotherapy and onset of hematuria, delay in initiation of HBOT after start of hematuria, prior need for transfusions, use of anticoagulation medications, and active smoking. The decreased effectiveness of HBOT treatment with most of these risk factors is likely related to a higher initial disease burden in these patients and delay in treatment. Risk factors for recurrence of symptoms have also been studied and include higher radiation dose, higher number of HBOT sessions in initial treatment, shorter interval between completion of radiotherapy and onset of hematuria, and delay in initiation of HBOT after start of hematuria. Again, this is likely related to a higher initial disease burden in these patients.

As a delay in initiating HBOT after the start of hematuria is a risk factor for decreased effectiveness of HBOT and support the earlier use of HBOT in treating hemorrhagic cystitis. Chong et al. found that 96% of patients had complete or partial resolution of symptoms if treated within 6 months of the onset of hematuria.[25] In contrast, only 66% of patients had complete or partial resolution of symptoms if treatment started more than 6 months after the onset of hematuria.

Figure 1



Novel approaches

Given the lack of evidence supporting a single therapy for RC, investigators are continuing to investigate novel methods that might play a therapeutic role in the future. Tacrolimus is an immunosuppressive agent that can be used systemically or topically. In wound care, topical tacrolimus is used in the treatment of pyoderma gangrenosum, among other inflammatory based wounds.[26] A liposomal based intravesical tacrolimus is being evaluated for the treatment of RC. While mostly case studies at present, larger phase 2 trials are ongoing.[12,27] Intravesical hyaluronic acid was studied against hyperbaric therapy, both demonstrated improvement, but hyaluronic acid significantly improved voiding frequency at 12 months.[28] Investigation is underway to try to find a laser protocol that is more focused, and minimizes collateral damage to the bladder lining. One such example is Greenlight® (American Medical Systems) laser light with potassium-titanyl-phosphate crystals.[29] Animal models are being used to investigate angiogenesis therapies such as vascular endothelial growth factor therapy as well as the injection of endothelial cells.[30] Finally, genetic analysis of patients who have cancer and are about to undergo neoadjuvant therapy may provide insight into populations at a particularly high risk for radiation complication and might alter treatment plans.[31]

Cost Effectiveness of HBOT

One of the hesitations some providers express when considering HBOT is the perception of increased cost. To provide insight into that concern, a group of researchers, using the CMS claims data-base, published a paper comparing the cost for hyperbaric therapy compared to standard of control in a population of 3,309 patients.2 This was a claims based retrospective study that evaluated claims between 2014-2019. A one-year look back, prior to the diagnosis of RC, was conducted to evaluate medical costs for both the hyperbaric group and the control group. The authors then followed the cost of treatment and followed the patients in both groups for one year post therapy. As with other conditions treated with hyperbaric, there was a correlation with better clinical outcomes and reduced overall cost, when patients received the full course of therapy. (Table 1.) The paper provides support for the cost-effective outcomes and long-term clinical results. The study was not randomized, and patients were only followed for one year post therapy.

Table 1

	base model hyperbaric treatments ≥ 1	hyperbaric treatments ≥ 20	hyperbaric treatments ≥ 30	model at recommended dose hyperbaric treatments ≥ 40
hyperbaric study group (N)	1,030	695	693	330
comparison group (N)	2,279	2,279	2,279	2,279
dependent variables	percentage difference	percentage difference	percentage difference	percentage difference
total spending	-$3,267 (10% ↓ *)	-$8,274 (27% ↓ ***)	-$10,868 (34% ↓ ***)	-$11,548 (37%↓ ***)
inpatient spending	-$3,188 (22% ↓ **)	-$6,686 (46% ↓ ***)	-$8,221 (55% ↓ ***)	-$9,222 (60%↓ ***)
physician spending	-$1,114 (14% ↓ **)	-$1,358 (17% ↓ ***)	-$1,760 (22% ↓ ***)	-$1,149 (15%↓ ***)
endoscopic treatment [Y/N]	(30% ↓ ***)	(33% ↓ ***)	(31% ↓ ***)	(34%↓ ***)
number of endo-scopic procedures	(44% ↓ ***)	(37% ↓ ***)	(33% ↓ ***)	(39%↓ ***)
urinary bleeding (with radiation cystitis dx) [Y/N]	(27% ↓ ***)	(31% ↓ ***)	(31% ↓ ***)	(36%↓ ***)
blood transfusion [Y/N]	- (not significant)	(57% ↓ ***)	(91% ↓ ***)	(78%↓ **)
mortality [Y/N]	(18% ↓ **)	(46% ↓ **)	(56% ↓ ***)	(53%↓ ***)

note: *** indicates significant at 1%, ** indicates significant at 5%, * indicates significant at 10%

Summary and Conclusion

In summary, radiation cystitis and hemorrhagic cystitis can occur in both men and women after pelvic radiotherapy for a variety of cancers. It, along with other delayed radiation injuries, is one of the more common indications for HBOT utilization. There is currently no gold standard treatment for radiation cystitis, with many of the treatment options either providing only short-term resolution or carrying significant morbidity and mortality risks. Given the current understanding of delayed radiation-induced injury, HBOT provides therapeutic effects that directly counteract hypoxia and fibrosis to promote tissue healing and angiogenesis. There is mounting evidence that HBOT offers both short-term and long-term improvement in both subjective clinical findings

of HC and patient-reported outcomes for RC. In addition, HBOT does not cause damage to the bladder mucosa, as might be the case with other treatment options, and it does not limit the ability to utilize other modalities in conjunction with hyperbaric oxygen therapy. In contrast to previous treatment algorithms for HC that show HBOT as a second- or third-tier option, evidence supports the early use of HBOT in these patients to improve clinical outcomes.

This white paper provides education on the current treatment recommendations for radiation cystitis and how HBOT can be an evidence-based treatment modality for these patients.

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