UNDERSEA & HYPERBARIC MEDICINE

Controlled CMS Data Demonstrates a Cost and Clinical Advantage for Hyperbaric Oxygen for Radiation Cystitis

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ABSTRACT

Feldmeier J, Kirby J, Gelly H, Robins M, Peters J, Gruhn P, Pal S. Controlled CMS Data Demonstrates a Cost and Clinical Advantage for Hyperbaric Oxygen for Radiation Cystitis. Undersea Hyperb Med. 2024 Second Quarter; 51(2):145-157.

Introduction: Increasing cancer survivorship, in part due to new radiation treatments, has created a larger population at risk for delayed complications of treatment. Radiation cystitis continues to occur despite targeted radiation techniques.

Materials and Methods: To investigate value-based care applying hyperbaric oxygen (HBO_2) to treat delayed radiation cystitis, we reviewed public-access Medicare data from 3,309 patients from Oct 1, 2014, through Dec 31, 2019. Using novel statistical modeling, we compared cost and clinical effectiveness in a hyperbaric oxygen group to a control group receiving conventional therapies.

Results: Treatment in the hyperbaric group provided a 36% reduction in urinary bleeding, a 78% reduced frequency of blood transfusion for hematuria, a 31% reduction in endoscopic procedures, and fewer hospitalizations when study patients were compared to control. There was a 53% reduction in mortality and reduced unadjusted Medicare costs of $5,059 per patient within the first year after completion of HBO_2 treatment per patient. When at least 40 treatments were provided, cost savings per patient increased to $11,548 for the HBO_2 study group compared to the control group. This represents a 37% reduction in Medicare spending for the HBO_2-treated group. We also validate a dose-response curve effect with a complete course of 40 or more HBO_2 treatments having better clinical outcomes than those treated with fewer treatments.

Conclusion: These data support previous studies that demonstrate clinical benefits now with cost-effectiveness when adjunctive HBO_2 treatments are added to routine interventions. The methodology provides a comparative group selected without bias. It also provides validation of statistical modeling techniques that may be valuable in future analysis, complementary to more traditional methods.

Keywords: contemporaneous cohort controlled; cost savings; hyperbaric oxygen; late radiation effects; Medicare payment; radiation cystitis

INTRODUCTION

Cancer survivorship has increased dramatically over recent decades in part due to the increased application and technological improvements of radiation therapy in treatment protocols, which are often multidisciplinary [1]. The American Cancer Society estimates that about 714,000 cases of pelvic malignancy occur annually in the United States [1]. More than 50% of these are likely to receive radiation as part of their cancer management. Modern radiation techniques and advanced technologies have allowed dose escalation, which has surely contributed to improved tumor control, especially in prostate cancer. Many in the radiation oncology community had predicted superior tumor control and reduced serious toxicity with the newer targeted techniques, prominently including intensity-modulated radiation (IMRT). [2,3]

However, late toxicity involving normal tissues still occurs despite new modern targeted techniques. In part, the failure to achieve decreased toxicity may be due to the increased radiation dose that has become the standard of care in many tumors, especially for prostate cancer. Pelvic radiation, in many instances curative, still can cause damage to adjacent normal tissues in some patients. Several reviews do indeed show a reduction in rectal complications when using newer techniques, but for bladder toxicity, the results are not clearly improved. Recent papers report nearly identical incidences of bladder complications with conformal radiation (an older tumor-targeting technique) and IMRT [4]. The reported incidence of bladder late radiation tissue injury (LRTI) in recent studies varies from about 7% to 11 % [5-8] and to perhaps as high as 13%.

A very telling statistic is reported in the Ma paper [5], which prospectively reviewed 1,198 consecutive patients admitted to a tertiary hospital urology service over six months. Twenty-three percent of all emergency urologic admissions in this review were attributable to radiation therapy complications. Radiation cystitis can be a chronic problem that requires multiple hospitalizations, several endoscopic and invasive procedures, multiple transfusions, diminished quality of life, and even death.

The review of 709 patients by Martin et al. [7]. provides additional perspective here, reporting that radiation cystitis patients require an average of 2.5 admissions and an average hospital stay of 7.6 days (range 1-42 days). Fifty-two percent require a blood transfusion of an average of 4.3 units. These patients underwent procedures including cystoscopy with fulguration +/-clot evacuation in 86% of cases. Four of their 709 subjects died due to radiation cystitis. In another publication, Linder et al. [9] reported a 16% mortality for patients undergoing urinary diversion and cystectomy when the bladder is deemed to be unsalvageable due to the persistence and severity of late effects of radiation injury.

The National Cancer Institute (NCI) has developed a widely employed reporting and grading system for cancer treatment adverse effects and continues to update it to grade the severity of complications. This system is called the Common Terminology Criteria for Adverse Events (CTCAE) [10]. Many publications emphasize Grades 3 and 4 CTCAE damage in their studies of cystitis because, at these levels, the severity of symptoms requires intervention to restore quality of life and/or preserve life.

Our understanding of the pathophysiology of late radiation effects on normal tissue has been historically attributed to vascular injury of the irradiated tissues characterized by endarteritis with resultant tissue hypoxia and attendant tissue damage [11-13]. More recently, some experts have proposed a model known as the Fibroatrophic Effect [14]. In this model, delayed radiation injury evolves due to apoptotic cellular depletion of parenchymal cells and stem cells within tissues and organ systems. Actively functioning cells are replaced by fibrous amorphic, avascular, and acellular tissue fields. The two models are not mutually exclusive. Inadequate vascularity can result from fibrosis replacing normal functional tissues [15], and chronic tissue hypoxia caused by vascular compromise can result in tissue fibrosis [16]. The described mechanisms of both models result in a positive feedback loop that promotes and perpetuates chronic delayed damage. Hyperbaric oxygen has been demonstrated to benefit all three elements of the established pathophysiology of LRTI. It enhances angiogenesis, stimulates stem cell production, and reduces fibrosis [17].

Pascoe and colleagues [18], after reviewing 23 papers on the topic, published a manuscript providing guidelines and an algorithm for managing radiation cystitis. They discuss cystoscopy with clot extraction, irrigation, chemical, laser, argon coagulation, chemical cautery, and hyperbaric oxygen, although hyperbaric oxygen is not introduced until after more conservative interventions have failed. They also admitted that there is a dearth of Level 1 evidence supporting any of these interventions.

Hyperbaric oxygen has been used to treat radiation cystitis for several decades [19-25]. These publications consist mostly of fairly small clinical series. Results have been consistently positive, but the level of evidence is low. Oscarsson and co-authors have recently [26] reported a multicenter phase 2-3 randomized controlled trial in 2019. The study was conducted employing the Expanded Prostate Index Composite Score (EPIC), a patient self-accomplished quality of life questionnaire. The hyperbaric group improved by 10.1 points on the serial EPIC assessment compared to 7.7 points for the non-hyperbaric group. The comparison of these changes was statistically significant.

The present study utilizes Medicare claims data to compare the clinical outcomes as reconstructed from billing codes and the cost-effectiveness of using hyperbaric oxygen therapy to treat radiation cystitis versus conventional care. Using de-identified billing records and without access to the clinical records, we reconstructed the clinical course and cost to Medicare for treating 3,309 patients between 2014 and 2019. In this fashion, a large experience contrasting treatment with and without hyperbaric oxygen was made available for analysis. Note where billing quotes are presented in this paper, they include both the Medicare payout and the patient copays.

MATERIAL AND METHODS

Database construction

This study employed Medicare Part A and Part B fee-for-service (FFS) claims for patients with radiation-induced cystitis. Claims included data for inpatient, outpatient, durable medical equipment (DME), home health agency (HHA), hospice, and skilled nursing facility (SNF), as well as carrier administrative data, including Medicare beneficiary demographic and enrollment-related data from the Master Beneficiary Summary File (MBSF) for the period from October 1, 2014, through December 31, 2019. These data were used to construct a study group of beneficiaries who received hyperbaric oxygen treatment (HBO_2) and a control group who received only non-hyperbaric care, which included primarily conservative care with irrigation, clot extraction, and cautery for their radiation cystitis. A lack of accurate coding resulted in some cases not being identified, and we felt that it was reasonable to include patients with diagnoses of both chronic cystitis and hematuria, along with a history of pelvic malignancy. All aspects of patient privacy were protected per HIPPA regulations by virtue of the study design, and all information was de-identified without access to clinical records. For inclusion, subjects had to have at least two non-laboratory or non-imaging billings consistent with radiation cystitis. The vast majority of both groups and essentially all of the study group, had been coded with a diagnosis of radiation-induced cystitis. We know that the subjects receiving hyperbaric oxygen were almost certainly coded properly because only those with late effects of radiation would be covered by Medicare.

Beneficiaries were excluded from the analytic file if they had radiation proctitis or had received active cancer treatment less than three months before their enrollment. In instances where a beneficiary had more than one eligible episode of HBO_2 over the study period, the longer episode was included in the analysis. In instances where more than one course of hyperbaric oxygen was completed, almost always the second course was the longer of the two, and consistently, the first course was very short, typically consisting of one or two treatments.

The focus was on beneficiaries with chronic delayed radiation cystitis for which standard treatments had not resulted in remission. To be considered in remission after treatment, there needed to be six months or more without cystitis-specific additional therapeutic interventions, including transfusion.

For both the study group and the control group, the analysis consisted of 3 distinct time periods or phases. Initially, all Medicare records available to us were scanned to identify procedures and tests consistent with radiation cystitis. These included bladder endoscopic procedures or surgical interventions, clot retraction, and bladder irrigation and transfusions. Once the diagnosis of cystitis was made, a one-year pre-treatment review was done to establish baseline Medicare expenditures for all enrolled patients. This pre-treatment phase constituted Phase 1 for both groups. The second phase was the treatment phase, wherein for both the study group and the control group, the costs specifically related to cystitis treatment were identified. Phase 3 was the one-year follow-up for both the study and control groups. In both Phase 1 and 3, total Medicare outlays were reviewed and compared. Figure 1 provides a quick visual depiction of the study design and sequence.

Our inclusion of all Medicare payments in Phase 1 and Phase 3 incorporated the cost of comorbidities and included all therapeutic interventions. For the HBO_2 study group, the treatment phase (Phase 2) began on the first day, ended on the last day of hyperbaric treatment, and was 81 days on average. The hyperbaric oxygen phase was considered complete if there was a four or more months break between HBO_2 treatments.

For the non-hyperbaric group, Phase 2 began when billings were also consistent with the onset of radiation cystitis. When modeling was done, the length of the treatment group, Phase 2, for the control subjects was initially set at 97 days as an estimate based on preliminary findings. Because of a wide variation in clinical response to treatment, it was decided not to apply this information in calculating differences in the cost of treatment.

Other interventions for radiation cystitis would continue for both groups and be quite variable for each patient until and if there was a remission. Because some patients would continue to have cystitis symptoms beyond the defined and modeled Phase 2 definitions of the treatment period and well into the follow-up period, we decided that the most appropriate and relevant financial comparison of treatment expenses would be the cost of the hyperbaric treatments, which was unique to the study group. Certainly, for the study group, these would have the largest impact on the expenditures during that phase. Both groups would continue to have other expenses, including cystoscopies, fulgurations, transfusions, etc. However, since the study group ultimately showed significant clinical improvements comparatively, these interventions and their attendant costs in this group would decrease more on average over time than the costs of those interventions for the control group. A previously cited review paper had recommended 40 hyperbaric treatments routinely for radiation injuries.[17] In order to calculate the Medicare-authorized reimbursement for a typical course of hyperbaric treatment, the number 40 was multiplied by the daily authorized Medicare

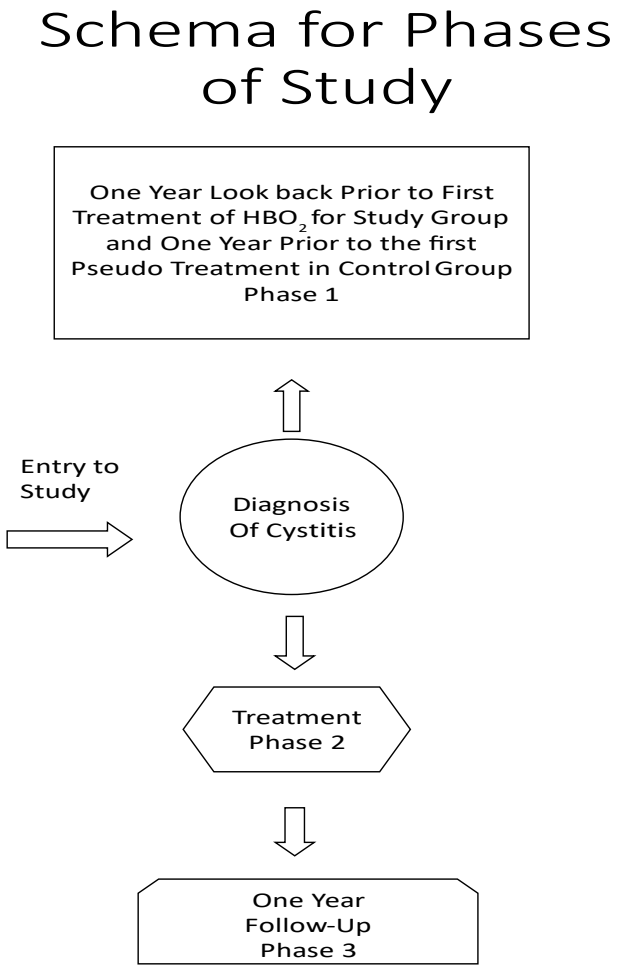

Figure 1. **This Schema provides a pictorial depiction of the Study Activities and Timing of Various Phases.**

reimbursement for a single hyperbaric treatment, including the physician's fee. The total expenditure for 40 hyperbaric treatments would be just about $25,000.

Statistical design and analysis

For analysis, we used Difference-in-Differences (DiD) modeling to evaluate the effect of HBO_2 on Medicare spending as well as for other outcome measures, including the incidence of bleeding, the need for transfusion, the number of transfusions, and the record of urologic endoscopic procedures. For other metrics, the DiD model was applied separately. Finally, using a linear probability model, we examined whether there was any difference in mortality rate between the study and control groups.

The main statistical challenge arises from the fact that patient assignment to treatment or control group is not random. Self-selection could be expected to increase entry into the HBO_2 study group. Other factors, observed (e.g., health status or comorbidities) and unobserved (e.g., mental stress or family background), could have also affected the number of patients seeking hyperbaric treatment.

There may also be a physician bias in referring only more severely affected patients for hyperbaric oxygen due to the perceived increase in expense when HBO_2 is employed. Several review articles, including clinical practice guidelines, do not include consideration of hyperbaric oxygen until most or all other common interventions have failed. We used an inverse probability of treatment weighting (IPTW) propensity score model to address the non-randomness issue. [27].

The IPTW method has several advantages [27-30]. The over-expressed weight of the control group is weighted down [28]. The IPTW approach uses the entire cohort and can address a very large number of confounding variables, and in doing so, it provides increased precision and representativeness [28,29]. Additionally, IPTW requires fewer distributional assumptions about the underlying data and avoids the potential residual confounding that arises from stratification on a fixed number of strata [30].

To address the potential self-selection issues, we estimated the Propensity Score model to assign appropriate weights to each of the comparison group and treatment group beneficiaries. [31-33] This method allows observational studies to be designed similarly to randomized experiments. We have also performed the Balanced Diagnostic Test to ensure that the observed baseline covariates are similar between the treatment and comparison groups. [34] We used the Standardized Mean Difference statistic to confirm that the covariates are balanced between these two groups at the baseline period. The balanced diagnostic test result suggests that all the covariates satisfy this diagnostic test in the base year since the absolute value of the standardized mean difference of all the explanatory variables is less than 0.25. Please reference Table 1.

RESULTS

Results are included below in two major categories and summarized in Tables 2 and 5. The first is a cost comparison of Medicare payments in the three phases. In Phases 1 and 3, both one-year periods, the comparison was made for average total Medicare outlays for both groups. See Table 2. For Phase 2, it was felt that the most pronounced difference in billings was the cost of the hyperbaric treatments and that the other cystitis-specific interventions would be comparable or reduced in the study group as more hyperbaric treatments were completed. Such a reduction would offset some of the expenses incurred by the hyperbaric treatments. A more specific comparison of these relative outlays is not possible due to the ongoing interventions for radiation cystitis in those who were not brought into remission in either group. Our modeling was not designed to provide this information. We note that the costs of continued specific interventions for unresolved cystitis are included in the total expenditures incurred during the one-year follow-up period. As noted earlier, these payments would include cystitis-specific interventions.

We found that the hyperbaric group was more likely to carry a diagnosis of hematuria and more likely to require transfusion in Phase 1. These findings suggest that the hyperbaric group included patients with more severe radiation cystitis. See Tables 3 and 4. Notably, the HBO_2 group also had higher

without weight				with IPTW weighting				
hyperbaric group (1,030)		control group (2,279)		hyperbaric group (1,030)		control group (2,279)		
explanatory variables	mean	explanatory variables	mean	explanatory variables	mean	explanatory variables	mean	balanced diagnostic test
age	76.59	age	76.90	age	76.76	age	76.92	-0.02
female	8.06%	female	25.81%	female	21.33%	female	31.41%	-0.23
dual	5.15%	dual	13.08%	dual	12.98%	dual	15.50%	-0.07
white	85.92%	white	89.30%	white	88.08%	white	89.98%	-0.06
black	9.51%	black	6.54%	black	7.27%	black	5.91%	0.05
asian	0.78%	asian	1.00%	asian	0.86%	asian	1.06%	-0.02
hispanic	0.97%	hispanic	0.82%	hispanic	1.05%	hispanic	0.80%	0.03
north american native	0.19%	north american native	0.17%	north american native	0.31%	north american native	0.18%	0.02
others	2.62%	others	2.17%	others	2.42%	others	2.07%	0.02
CCI	0.46	CCI	0.47	CCI	0.45	CCI	0.48	-0.06

compares pre-treatment demographics and the Charlson Co-morbidity Index for both unweighted and weighted study and control groups. both groups are well-matched in each category, as demonstrated by the Balanced Diagnostic Test, which reflects the validity of the weighting and subsequent statistical determinations.

Table 1. Summary of Covariates and Diagnostic Test in Pre-Period for HBO_2 and Comparison

study (HBO_2)	$31,293	$26,234	-$5,059 (any hyperbaric treatment)
control	$29,130	$31,496	+$2,366
difference (HBO_2 minus control)	$2163	-$5261	-$7425

presents total Medicare-authorized payments for both groups, comparing post-treatment to pre-treatment (phase 3-phase 1) The entries suggest a more severe initial level of disease in the study vs control group with $2163 additional charges. at the one-year follow-up, the average savings for the study group at all hyperbaric dose levels equals $5059. note in the table a minus sign indicates a savings and a + sign represents an increased Medicare-authorized payment.

Table 2. Average Total Annual Patient Medicare Authorized Payments

radiation cystitis with urinary bleeding	phase 1. pre-treatment
study group	63.6%
control group	14.9%
difference (study-comparison)	48.7%

shows that the occurrence of hemorrhagic cystitis is more than four times more likely to occur in the study group than in the control group during the pretreatment phase strongly suggesting more severe disease.

Table 3. Incidence of radiation cystitis with bleeding for each group during Phase 1

percentage requiring blood transfusion	phase 1 (baseline pretreatment)
study group	10.4%
control	5.1%
difference (study-comparison)	5.3%

demonstrates that transfusion during phase 1 is twice as likely in the hyperbaric group compared to control suggesting more severe disease.

Table 4. Percent of patients receiving blood transfusion during Phase 1 (Pre-treatment)

billings than the control during Phase 1 (pre-treatment). These higher payments for the hyperbaric group during Phase 1 also suggest that the study group started with more serious radiation complications on average at entry.

Table 5 shows several important comparisons. Control patients are compared to hyperbaric patients treated at four increasing hyperbaric dose points: one or more treatments, more than or equal to 20 treatments, more than or equal to 30 treatments, and more than or equal to 40 treatments. Analyses at these dose points show better results as the number of treatments is increased sequentially to 40 or more. The figures in the parentheses indicate the percent change relative to the mean

value of the respective dependent variables in the pre-treatment period (except for mortality). The mortality analysis was based on a linear probability model, so the figures reflect the percent change relative to the mean value of the comparison group in the post-treatment period.

As shown in Table 5, total Medicare spending in the post-treatment period relative to the mean value in Phase 1 (pre-period) among patients in the HBO_2 study group who received at least 40 treatments was $11,548 lower than the change in spending for the control group patients during the same period, a reduction in spending of about 37%. This finding was significant at the 1% level. The spending reduction was primarily driven by lower inpatient hospital spending of $9,222 and lower physician services-related spending of about $1,149, a reduction of 60% and 15%, respectively. These reductions in spending were also significant at the 1% level. As shown in the analyses of the subgroups divided according to the number of hyperbaric oxygen treatments, the savings to Medicare increased as the number of treatments increased in almost all clinical outcomes.

By the first year post-HBO_2, the unadjusted Medicare payments for Phase 3 (follow-up) were $5,059 lower across the board for any patient receiving any number of hyperbaric treatments. The Difference in Differences regression modeling compares the pre-and-post-treatment financial outlays in both the study and control groups internally. When patients received the recommended 40 or more hyperbaric treatments, the total Medicare payments decreased by more than $11,548 per patient compared to the control group. [17] Interestingly, the majority of our patients received fewer than 40 treatments. Phase 3 costs for the control group were higher than Phase 1 in the control group, suggesting little response or even worsening cystitis with standard treatment. See both Table 2 and Figure 2 and their legends.

	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 endoscopic 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%
shows specific financial and clinical results comparing the results for the hyperbaric group overall to the control group for the same time period and at additional intervals of 20 or more hyperbaric treatments, 30 or more treatments, and 40 or more treatments. even at 1 to 20 treatments, there was a clinical and financial advantage. all dollar amounts are for a 12 month period per individual patient.

Table 5. Overview of Additional Clinical Results with Increasing Number of Treatments

In addition to Medicare spending, we also examined and compared a number of key clinical outcomes. As shown in Table 5., patients in the HBO_2 study group had consistently better outcomes relative to the pre-treatment period. For example, patients in the HBO_2 study group at one-year follow-up (phase 1) relative to the same group in Phase 1 (Pre-treatment) had:

- a 53% reduction in mortality, significant at the 1% level;
- a 78% reduction in the probability of receiving a blood transfusion, significant at 5%;
- a 39% reduction in the number of endoscopic procedures, significant at 1%;
- a 31% reduction in patients receiving any endoscopic procedure, significant at the 1% level;
- a 5% reduction in the probability of having a urinary bleeding diagnosis, with an average 36% reduction in urinary bleeding among patients with a coded diagnosis of radiation cystitis with bleeding. This finding was significant at the 1% level.

Although this study shows more overall Medicare savings in Phase 3 when the number of HBO_2 treatments equals or exceeds the standard of care of 40 or more, even with fewer treatments, patients who receive HBO_2 have better outcomes than those who do not receive any number of HBO_2 treatments.

DISCUSSION

The study provides clinical support and economic justification for using hyperbaric oxygen to treat chronic radiation-induced cystitis. All clinical outcome parameters compared to standard care (Table 5) show that hyperbaric oxygen is more effective than traditional interventions. Analyses in Table 5 also support a clear dose response, demonstrating that patients had better clinical outcomes at 40 treatments or more than at fewer treatments. Thirty to 60 hyperbaric treatments for radiation injuries have been previously recommended by an extensive review article in 2012.[17]. Because of its claims-based design, our study does not allow us

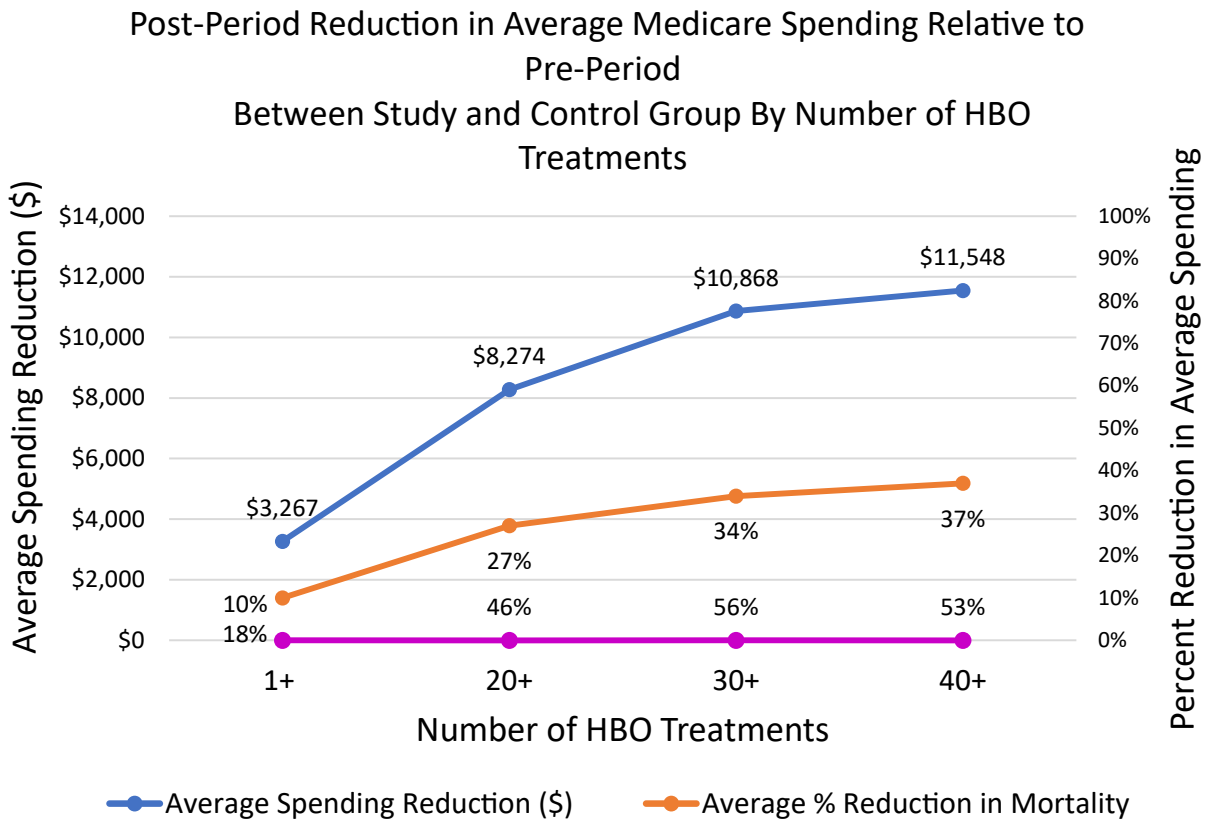

Figure 2. On this graphic plot the orange line provides the percentage savings compared to pre-treatment for the Hyperbaric Group. The blue plot provides the same savings in dollars which are nor corrected for inflation.

to compare specific hyperbaric protocols, including treatment pressures or duration of individual treatments. We note that fewer than our study patients actually received 40 or more treatments.

Reductions in Medicare outlays for the Study Group across all doses equal the $5,059 decrease in the Study Group. This advantage increases with increasing numbers of hyperbaric treatments. For the group receiving at least 40 treatments, this advantage has increased to $11,548 in the first year. Without additional years of follow-up, we cannot project the savings in the second year or beyond. However, it is notable that nearly one-half (46%) of the cost of the hyperbaric treatments was recouped in the first year.

Smart and Wallington [35] have demonstrated cost savings with a 2.5-year follow-up that are consistent with our findings and suggest a durable hyperbaric effect. Admittedly, the results of the current study would be stronger if we had a more extended follow-up period to analyze them. Further analysis of the data with a longer post-treatment study period would help clarify the longer-term financial impact. Even so, by one-year post-treatment, the advantage of hyperbaric treatments in comparative billings has recovered over the cost of hyperbaric oxygen.

Perhaps the most notable outcome of our study was a decrease in mortality in the hyperbaric-treated patients by more than 50% compared to control at one year. A review of the literature shows that the trend toward a decrease in mortality after hyperbaric oxygen treatments is not unique to our study. Löndahl [36]has previously reported an increase in survival associated with hyperbaric oxygen in his randomized controlled trial of hyperbaric oxygen for patients with diabetic foot ulcers. At six years follow-up, patients in this trial receiving HBO_2 had a survival of 63.2%, while non-hyperbaric controls had a survival of 40.5%. A more recent, non-randomized trial reports increased survival in patients receiving hyperbaric treatment of chronic osteomyelitis. In this cohort comparison study of 5,312 patients admitted to the hospital for chronic osteomyelitis authored by Thai and associates [37], overall survival was better for the hyperbaric treated group at one year compared to the non-randomized control group (3.8 % mortality vs 7.6%).

The Charlson comorbidity index (CCI) is used to predict one-year and ten-year mortality in study populations.[38] The CCI calculated for both groups before treatment demonstrated an excellent match for the presence of intercurrent diseases and predicted comparable mortality. Some might argue that those receiving hyperbaric oxygen in the intervention for chronic radiation cystitis represent a group not well-matched to non-hyperbaric patients and that patients referred for hyperbaric oxygen might represent a more favorable group. In fact, clinicians often employ hyperbaric oxygen as a last resort due to its perceived expense and inconvenience. The previous discussion in the results section provides evidence suggesting that hyperbaric oxygen is frequently reserved for more seriously injured patients. In our study, the likelihood of delayed referrals is borne out by the fact that approximately two-thirds of the patients we studied did not have hyperbaric treatment. Several publications recommend deferring hyperbaric oxygen application until all other interventions have failed. [39-43] As previously discussed, clinical practice guidelines frequently require "conventional" care failure before coverage of hyperbaric oxygen therapy can be provided. The National Coverage Determination 20.29, adopted by the Centers for Medicare and Medicaid Services, explicitly requires a lack of response to conventional therapy prior to adding hyperbaric oxygen treatments to the clinical protocol.[44] Our patient population was limited to those who were Medicare-eligible. Therefore, they likely failed multiple rounds of conventional care. The cost of their conventional care is shown in Table 4 for the time limits of the study, and the treatment arm has higher costs as compared to the control arm, arguing for more complexity and interventions. However, Chong et al. [45] have shown that early intervention with hyperbaric oxygen for radiation cystitis improves clinical outcomes. Pursuing ineffective treatments only adds to the cost of management.

This study employed a novel methodology for reconstructing medical interventions and comparing the Medicare-authorized payment for beneficiaries with chronic radiation cystitis. Employing the keywords "cost-effectiveness" and "Medicare payment

records" in a MEDLINE search, eight publications were discovered that address Medicare payment and a variety of clinical interventions in various disorders. [46-53] These study designs were compared to the methodology of this study. As opposed to the present study, these publications either had access to clinical records or used a simulated population. Many did not present a clinical outcome. In contrast, our access to Medicare payment data was employed to identify the actual clinical interventions in real patients and the reimbursed amounts for treating chronic radiation-induced cystitis.

Using this methodology, a total of 3,309 patients were identified and studied for the years in which Medicare payment records were available to us. Of these, 1,030 patients received hyperbaric oxygen, and 2,279 received traditional treatments only. Our study's analyzed cases far exceed even comprehensive review studies comparing the results of several common interventions at many clinical centers. By comparison, two comprehensive review papers had pooled patients of 985 and 1194 respectively. [18,54] Despite the novel study design, the methodology employed in the current study was straightforward, and validity is expected to be high. Patient self-selection or managing physician preference might have impacted the random nature of patients in the hyperbaric group. Previous discussion in the Materials and Methods section presents some statistical techniques employed to correct this possible bias. By combining all Medicare beneficiaries treated for chronic radiation cystitis during the period of the study, most, if not all, biases were excluded.

While some may question its evidentiary value because it is not an RCT, this study permits a comparative analysis of more than 3,000 patients with chronic radiation cystitis who met eligibility requirements treated over a period of 63 months without identifiable bias in selecting a control group or study group. While randomized controlled trials have been the gold standard for evidence-based medicine for several decades, they, too, have inherent weaknesses in their study design. In their paper, Saturni et al. [55] compared the advantages and disadvantages of both randomized controlled trials and studies based on real-world data. They note that RCTs limit their enrollment to a select group of eligible subjects that may not represent the population at large. Additionally, they observe that there are ethical considerations when control groups are randomized to no therapy or therapies that are clearly less effective. Very few studies address the outcomes that are achieved in the "real world," where practice patterns may vary according to availability and no patient is excluded based on their existing comorbidities unless those co-morbidities would be a contraindication to hyperbaric exposure. Our study accepted all identified patients except for those having had recent cancer treatment or those who had radiation-induced proctitis in addition to cystitis.

Recommendations

In summary, this paper utilized a large-scale public database of Medicare payments. This study showed both a clinical and economic benefit to post-irradiation cystitis patients who were referred for hyperbaric oxygen treatments and who received the recommended forty treatment protocols. There were demonstrable reductions in endoscopy transfusions and decreases in hospitalizations when adjunctive HBO treatment was added to conservative therapies. The use of this novel statistical modeling may contribute to valuable comparative clinical effectiveness research. Such methods may complement traditional clinical research efforts, such as RCTs, as they help uncover clinical improvements and future research targeted at lower costs. Moore and colleagues have reported the costs of pivotal randomized controlled trials. [56] Based on their investigation, a controlled urologic trial with a similar enrollment would cost at least $12 million dollars. This study was conducted at a fraction of the cost of an RCT enrolling this many patients. This study demonstrates a dose-response curve effect for adjunctive HBO_2 in patients with post-irradiation cystitis where more complete HBO_2 treatment protocols (greater than equal to 40 HBO treatments) have better outcomes and lower Medicare billings at least during short-term follow-up. See a graphic plot of these savings in Figure 2. The authors recommend that patients be authorized to receive the full forty treatment course of hyperbaric oxygen.

Earlier intervention might reflect even greater clinical and economic impact, although these data reflect the current practice standard of failing conventional care prior to initiation of hyperbaric oxygen treatments. The authors recommend the utilization of hyperbaric oxygen earlier in the treatment of radiation cystitis treatment algorithms. In addition, more widespread acceptance of hyperbaric oxygen as part of the treatment protocol will impact the clinical trajectory of radiation cystitis patients, many of whom are prisoners of their bladders and have a diminished quality of life. Unsuccessful treatment of radiation cystitis is a costly and sometimes lethal complication of pelvic radiation.

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