Original Paper

Urologia Internationalis

Urol Int 2012;89:208–214
DOI: 10.1159/000338910

Received: August 31, 2011
Accepted after revision: April 7, 2012
Published online: July 10, 2012

Hyperbaric Oxygen Therapy for Radiation Cystitis in Patients with Prostate Cancer: A Long-Term Follow-Up Study

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Key Words
Hematuria · Radiation injury · Hyperbaric oxygen · Prostate cancer

Abstract
Objective: To assess the safety and efficacy of hyperbaric oxygen (HBO) for treating radiation cystitis a long-term follow-up study was done in patients with prostate cancer, the second most common malignancy in Japan. ***Patients and Methods:*** A total of 38 patients at an age of 68 ± 8 years with radiation cystitis following irradiation of prostate cancer were treated with HBO at 2 absolute atmospheric pressures for 90 min daily. The average number of HBO treatment sessions in each patient was 62 ± 12. The follow-up period was 11.6 ± 3.7 years. We evaluated objective and subjective symptoms periodically with special reference to the initiation timing of HBO therapy. ***Results:*** High efficacy ratios of objective and subjective findings were obtained at 2 and 4 (79–95%) years, respectively. After 7 years' follow-up, these ratios decreased slightly (72–83%) but still remained stable thereafter (75–88%) without any serious accident. Comparison of late morbidity scores before and 11.6 years after HBO therapy showed significant improvement ($p < 0.0005$). Twenty-eight patients (74%) obtained nonrecurrent outcome. They had received 18% lower ($p < 0.001$) radiation dosage than recurrent patients. The interval between the onset of hematuria and start of HBO treatment in nonrecurrent patients was 30% shorter ($p < 0.001$) than that of recurrent patients. ***Conclusions:*** We elucidated the long-term safety and beneficial effect of HBO therapy of radiation cystitis in patients with prostate cancer. Early application of HBO treatment after the onset of hematuria appears to produce favorable outcome.

Introduction

In the era of high-tech radiotherapy such as intensity-modulated radiotherapy, image-guided radiotherapy and particle therapy, the incidence of radiation cystitis has been decreasing [1–4]. Zelefsky et al. [1] reported the incidence of grade 2 and 3 urinary toxicities was 9 and 3%, respectively, in 561 patients who received a dose of 81 Gy to the prostate. However, long-term injury may occur in a small proportion of previously treated patients [2]. One of the most serious symptoms of radiation cystitis is severe hematuria; it frequently necessitates hospitalization and successive blood transfusion treatments. This condi-

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Table 1. Toxicity criteria of radiation cystitis according to the SOMA scale [10], modified by Veerasarn et al. [11]

Symptoms	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Objective symptoms					
Appearance of hematuria	none	occasional	intermittent	persistent	ungovernable
Urine RBC/HPF	<10	10–49	50–99	>100	>100
Requirement of blood transfusion	none	1–2 U	3–4 U	5–6 U	>7 U
Cystoscopic findings	normal	slight telangiectasia	telangiectasia, local hyperemia	diffuse hyperemia, ulceration	diffuse hyperemia, multiple ulcerations, occasional fistula
Subjective symptoms					
Miction pain	none	occasional	intermittent	persistent	ungovernable
Urination frequency, h interval	>3	2–3	1–2	0.5–1	<0.5
Bladder irritability	0	25	50	75	100

tion is occasionally life threatening, and reduces quality of life. Unfortunately, there has been very limited advance in the treatment of this hampered disease. Weiss et al. [5] have shown the feasibility of hyperbaric oxygen (HBO) treatment for patients with radiation-induced hemorrhagic cystitis. Low level of oxygen concentration and hypovascularity of the irradiated tissue and their reversal following HBO treatment have been demonstrated [6]. Except a few [5, 7], most of the previous HBO treatments were performed in a short period, but the time to symptom development was comparatively long and progressive [7]. Application of HBO for radiation cystitis is a recent treatment, and most previous investigators analyzed small numbers of patients in different pelvic cancer types, such as carcinoma of bladder, prostate, and uterine cervix. Except for a study of Bevers et al. [8], there are almost no large prospective randomized studies evaluating HBO for radiation-induced injuries. Although our data were reviewed retrospectively, we assessed the results of HBO treatment in patients with prostate cancer suffering from radiation-induced cystitis for a long time.

Patients and Methods

Between January 1988 and March 2011, a total of 38 patients with a mean age of 68 ± 8 years (range 49–82) with radiation cystitis were treated with HBO at our institute and followed for 7.4 to 19.2 years (mean 11.6 ± 3.7 years). Radiotherapy had been given for carcinoma of the prostate, and mean dosage was 67 ± 11 Gy (range 46–96). All patients had unsuccessfully undergone previous routine treatments to cease the radiation cystitis. They had hematuria and complained of miction pain, pollakisuria and bladder irritability. Cystoscopy was performed before the HBO therapy and after the completion of HBO treatment. After providing informed consent, patients received 100% oxygen in a multiple hyperbaric chamber. This therapy consisted of cycles of 90 min daily per treatment, 6 days per week, of HBO at 2 absolute atmospheric pressures. The average number of initial treatment sessions for each patient was 62 ± 12 (range 39–92). Thirty-two out of 38 patients (84%) required blood transfusions due to severe hematuria. Mean interval between final radiotherapy and onset of hematuria, mean interval between final radiotherapy and onset of HBO treatment, and mean interval between onset of hematuria and onset of HBO treatment are shown in table 3. Objective symptoms, such as appearance of hematuria, microscopic urinary sediment analysis, requirement of blood transfusion and cystoscopic findings were evaluated repeatedly during the follow-up period. Subjective symptoms, such as severity of miction pain, frequency of urination and bladder irritability were also assessed simultaneously. Parsons' questionnaires [9], slightly modified by us, were completed by patients after each HBO therapy to qualify the bladder irritability as score 0, 25, 50, 75, or 100. The objective and subjective symptoms before and after the HBO treatment were finally evaluated following the toxicity criteria for the bladder by the SOMA scale [10] with slight modifications [11] (table 1). For comparison of continuous variables, Student's t test (two tailed) was used. Wilcoxon singed-rank test was done to estimate pre- and post-HBO late morbidity scores using SPSS 11.5J computer program (Tokyo, Japan). Statistical significance was reached at $p < 0.05$.

Results

Table 2 shows the therapeutic results of HBO treatment in our patients. All patients had precedent hemorrhagic cystitis, and 32 (84%) of 38 patients required blood transfusion. Most patients no longer necessitated blood transfusion 11.6 years following HBO treatment. Similar favorable tendency was also observed in the degrees of red blood cell count in urine. The final grading score of urine cell count showed remarkable improvement ($p < 0.0005$). High efficacy ratio of cystoscopic findings was obtained at 2 (89%) and 4 (84%) years of follow-up. After 7 years follow-up, the efficacy ratio slightly decreased

Table 2. Symptom response to HBO treatment in patients with prostate cancer

Symptom	Improved cases/total cases					Toxicity grade of injury		
	2 years after HBO	4 years after HBO	7 years after HBO	10 years after HBO	11.6 years after HBO	grade	before HBO	after HBO
Objective symptom								
Hematuria appearance	36/38 (95%)	34/38 (89%)	33/36 (83%)	26/32 (81%)	26/32 (81%)	G0:	0	23
						G1:	0	2
						G2:	11	4
						G3:	19	3
						G4:	8	0
							$p < 0.0005$	
Urine RBC/HPF	35/38 (92%)	34/38 (89%)	28/36 (76%)	25/32 (78%)	24/32 (75%)	G0:	0	20
						G1:	1	6
						G2:	16	4
						G3:	18	1
						G4:	3	1
							$p < 0.0005$	
Requirement of BT, U	31/38 (82%)	30/38 (79%)	26/38 (81%)	24/32 (75%)	27/32 (84%)	G0:	6	25
						G1:	1	1
						G2:	5	4
						G3:	19	2
						G4:	7	0
							$p < 0.0005$	
Cystoscopic findings	34/38 (89%)	32/38 (84%)	27/36 (75%)	19/26 (73%)	26/32 (81%)	G0:	0	25
						G1:	11	4
						G2:	8	1
						G3:	17	1
						G4:	2	1
							$p < 0.0005$	
Subjective symptom								
Miction pain	35/38 (92%)	31/38 (82%)	26/36 (72%)	27/32 (84%)	28/32 (88%)	G0:	1	27
						G1:	2	2
						G2:	3	2
						G3:	27	1
						G4:	5	0
							$p < 0.0005$	
Frequency, h interval	34/38 (89%)	32/38 (84%)	30/36 (83%)	27/32 (84%)	25/32 (78%)	G0:	0	26
						G1:	3	4
						G2:	2	1
						G3:	26	1
						G4:	7	0
							$p < 0.0005$	
Bladder irritability	36/38 (95%)	33/38 (87%)	28/36 (78%)	26/32 (81%)	25/32 (78%)	G0:	0	23
						G1:	3	4
						G2:	5	3
						G3:	24	2
						G4:	6	0
							$p < 0.0005$	

Wilcoxon signed-rank test was used to calculate differences: see 'Materials and Methods'. For description of grades see table 1.

Table 3. Comparison of clinical characteristics between non-recurrent patients and recurrent patients with respective radiation cystitis

Patient characteristics	Nonrecurrent cases (n = 28)	Recurrent cases (n = 10)	All cases (n = 38)
Age, years	66 ± 5 (49–82)	69 ± 6 (57–82)	68 ± 8 (49–82)
Radiation dose, Gy	62 ± 11 (46–82)	76 ± 9* (58–96)	67 ± 11 (46–96)
HBO treatments	56 ± 11 (39–78)	75 ± 9* (58–92)	62 ± 12 (39–92)
Interval between final radiotherapy and onset of hematuria, years	4.0 ± 1.6 (1.7–9.1)	2.0 ± 0.9* (0.7–3.6)	3.5 ± 1.8 (0.7–9.1)
Interval between final radiotherapy and onset of HBO treatment, years	4.7 ± 1.6 (2.1–10.0)	4.4 ± 1.6 (1.9–6.6)	4.7 ± 1.8 (1.9–10.0)
Interval between onset of hematuria and onset of HBO treatment, years	0.7 ± 0.5 (0.1–1.8)	2.3 ± 1.2* (0.2–4.8)	1.1 ± 0.9 (0.1–4.8)

Data are presented as mean ± SD (range). * $p < 0.001$, significantly different from nonrecurrent group.

(75–81%), but successive follow-up at 11.6 years showed cystoscopic findings were improved ($p < 0.0005$). The high efficacy ratio of miction pain was obtained during the follow-up period except at 7 years. The toxicity grading score of the miction pain showed significant improvement ($p < 0.0005$). The HBO therapy resulted in rapid improvement of pollakisuria by 2 years and remained stable thereafter. Comparison of late morbidity scores before and after HBO was significant ($p < 0.0005$). Each patient complained of bladder irritability before HBO treatment. Bladder irritability ceased in 36 of 38 patients (95%) by 2 years after HBO sessions. Although efficacy ratios showed slight reduction after 7 years follow-up (78, 81 and 78% at 7, 10 and 11.6 years follow-up, respectively), analysis of the grading scores before and after HBO treatment showed a notable recovery ($p < 0.0005$).

Characteristics of patients with non-recurrent radiation cystitis and those with recurrent radiation cystitis are compared in table 3. Twenty-eight patients (74%) were classified as having non-recurrent outcome. They received 18% lower ($p < 0.001$) radiation dosage than recurrent patients. Thus, the number of HBO treatments of non-recurrent patients was 25% lower ($p < 0.001$) than in recurrent patients. Patients who had HBO treatment initiated at 0.7 ± 0.5 years after the onset of hematuria showed a significantly ($p < 0.001$) lower recurrence rate of radiation cystitis than subjects who were given HBO therapy at 2.3 ± 1.2 years after the onset of hematuria. During follow-up, some patients complained of occasional otalgia, but no patients were withdrawn from HBO therapy.

Discussion

One of the most prevalent urologic causes of radiation cystitis is pelvic radiotherapy for prostate cancer, as shown in 25% of cases by Bevers et al. [8], 65% by Mathews et al. [12], 82% by Corman et al. [13], 83% by Chong et al. [14], and 46% in our series. This cancer is the second most common pelvic malignancy in Japanese males, and close anatomical relationship between the prostate and urinary bladder may occasionally induce radiation injury of the bladder. The possible carcinogenesis of irradiated tissues may be of concern. First, high plasma concentration of active oxygen and subsequent free radical production following HBO treatment may enhance DNA chromosomal impairment [15]. Second, HBO treatment in rabbits demonstrated an eight- to ninefold increased vascular density over both normobaric oxygen and air-breathing controls [6]. These experiments suggest the efficacy mechanism of HBO therapy in radiation-induced injuries, but imply liable promotion of the carcinogenesis of the bladder. At present, however, the possibility that HBO may cause malignant development of irradiated tissues appears to be less likely by the fact that HBO did not accelerate indolent prostate tumor growth following the HBO treatment in animals [16], and Feldmeier [17] clinically showed significant differences between tumor vessels and wound healing angiogenesis with respect to growth and prohibition factors of the neoplasm.

In our study, HBO has shown long-term efficacy in objective and subjective symptoms of radiation cystitis (table 2). Thirty-five of 38 patients (92%) achieved improvement of urine red blood cell count within 2 years.

Table 4. Reports of HBO treatment for radiation-induced hemorrhagic cystitis in patients with prostate cancer

Report	Patients	Age years	Radiation Gy	HBO	Cure rate, %	Follow-up
Norkool et al. [22]	8	71 ± 8	63 ± 8	25 ± 8	83	18 ± 11 months
Weiss et al. [5]	6	70 ± 7	65 ± 2	58 ± 5	83	10 years
Bevers et al. [8]	10		63	20	100	29 months
Del Pizzo et al. [7]	4	70 ± 4	71 ± 2	39 ± 10	100	2.5 years
					25	5.1 years
Mathews et al. [12]	11	62	66		64	21 months
Mayer et al. [18]	8	71	50	26	82	15 months
Corman et al. [13]	50	70		33	86	10–120 months
Yoshida et al. [23]	4	66 ± 8	63 ± 6	18 ± 6	50	16 ± 12 months
Mohamad Al-Ali et al. [24]	7	81 ± 8	70 ± 0	30 ± 0	14	1.8 ± 1.6 years
Our study	38	67 ± 6	65 ± 12	60 ± 12	95	2 years
					89	4 years
					83	7 years
					81	10 years
					81	11.6 years

Thirty-six out of 38 (95%) patients also experienced the resolution of macroscopic hematuria following HBO treatment in the same follow-up period (table 2). The degree of late radiation morbidity before and after HBO was scored retrospectively in patients with prostate cancer by Mayer et al. [18]. Their 26 sessions of HBO treatment showed a significant improvement ($p = 0.004$) in macroscopic hematuria in 8 out of 11 patients (73%) for the average follow-up of 15.3 months [18]. By using a late radiation scoring criteria for radiation-induced hemorrhagic cystitis, 38 out of 48 patients (79%) showed complete or partial resolution of hematuria during at least 12 months follow-up [18]. In contrast to the positive effect of HBO on hematuria within 2 years in our study, a less beneficial effect of HBO was observed after 7 years, and persisted until the terminal follow-up period (table 2). However, the results of this study are still encouraging. It should be mentioned that most of the patients received HBO treatment after radiation cystitis had failed to respond to other traditional treatments.

Table 4 summarizes total HBO treatments for radiation cystitis in 146 patients with prostate cancer by previous investigators. Although there are extensive differences in treatment regimens, the HBO therapy suggests good short follow-up (<2 years) results, with a mean of 80% of patients having cessation or improvement of hematuria. In our study, other objective findings, such as requirement of blood transfusion and cystoscopic findings also showed that HBO was highly successful. Similar favorable outcome of other subjective symptoms was also obtained in our short follow-up study (table 2). Weiss et al. [5] followed 6 patients with prostate cancer for 10 years. These patients, at the age of 70 ± 3 years, had received 65 Gy of radiotherapy and were treated with 58 ± 2 HBO sessions, and 5 of 6 patients (83%) achieved asymptomatic status [5]. These results were almost identical to our 38 patients followed for over 11.6 years (table 2). In the present study, HBO has also produced a substantial benefit ($p < 0.0005$) in long-term improvement of subjective symptoms (table 2). Similar symptoms of radiation cystitis, such as dysuria, urinary frequency, urgency and macroscopic hematuria were examined by Mayer et al. [18], and satisfactory results were also demonstrated during 15.8 months follow-up. Del Pizzo et al. [7] reported the HBO treatment in 11 patients with radiation cystitis. During the median follow-up of 2.5 years, all patients showed improvement of hematuria (100%), but at the terminal follow-up of 5.1 years, complete cessation of symptoms was only 25% [7]. This suggests the progressive nature of radiation injury and its possible partial reversal by repeat HBO treatments. Indeed, repeat or intermittent HBO treatments reported by Mayer et al. [18] showed almost satisfactory results. Therapeutic results appeared to be also better in patients receiving 30 or more total HBO treatments as compared with fewer [19]. However, there are almost no prospective randomized trials evaluating the high frequent or intermittent HBO treatment for radiation injuries.

Favorable effects of HBO on radiation-injured tissue are considered to be induced by the hyperoxia-procured primary neovascularization and successive production of healthy collagen matrix [6]. Questions might be raised as to the precise mechanism of the sequence of the event. First, does the wound-healing ability still persist after the discontinuation of HBO treatment? Previously, HBO treatment for a limited period has been shown to enhance neovascularization in rabbits at the microscopic level [17]. Feldmeier [17] has also demonstrated evidence of improvement of fibrosis in the pelvic organs of mice receiving whole abdominal irradiation and subsequently receiving postirradiation HBO treatment compared to those treated with radiation alone. Such microangiogenesis probably induced by HBO treatment could create an oxygen gradient between the impaired hypoxic urothelium and the unimpaired environing healthy urothelium resulting in additional microvascularization [17]. Second, can the HBO treatment really raise the tissue oxygen tension of the impaired bladder tissue of the patients? We cannot answer this question precisely since neither bladder biopsy nor transcutaneous oxygen measurement has been systematically performed in this study. The tissue oxygen pressure in rabbit trigone before HBO treatment (72 ± 6 mm Hg) was gradually amplified following HBO treatment up to 504 ± 8 mm Hg at 53 min, and very slowly reduced in response to decreasing atmospheric pressures [20]. In a clinical study, HBO therapy consisting of 100% oxygen inhalation at 2 absolute atmospheric pressures daily for a relatively long period has been known to produce beneficial effect in ischemic or radiation-induced tissue injuries by fibroblast proliferation, enhancement of fibroblastic synthesis of collagen, noncollagenous protein and capillary formation [5, 21]. These animal experiments and clinical studies indicate that a relatively long HBO treatment increases oxygen tension in ischemic tissue and stimulates angiogenesis together with fibroblast proliferation, resulting in improvement of radiation cystitis. Our study might be criticized by recent investigators since the application of intensity-modulated radiotherapy or image-guided radiotherapy is helpful to treat defined malignant neoplasms without damaging healthy tissues. Therefore, reduction of radiation injuries, including late radiation cystitis, may be expected in the future. However, the majority of our patients with radiation cystitis are still living with or without life-threatening conditions. Long-term follow-up of these patients is necessary.

Acknowledgment

We thank Mr. Koji Kurihara and Ms. Kazumi Kanai at the Pharmaceutical Division of Kuriyama Central Hospital for statistical analysis.

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