Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–10, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.12.048

CLINICAL INVESTIGATION

HYPERBARIC OXYGEN TREATMENT OF CHRONIC REFRACTORY RADIATION PROCTITIS: A RANDOMIZED AND CONTROLLED DOUBLE-BLIND CROSSOVER TRIAL WITH LONG-TERM FOLLOW-UP

RICHARD E. CLARKE, C.H.T.,* L. M. CATALINA TENORIO, M.D.,† JAMES R. HUSSEY, PH.D.,‡ AKIN S. TOKLU, M.D.,§ D. LINDSIE CONE, M.D.,¶ JOSE G. HINOJOSA, M.D.,† SAMIR P. DESAI, B.D.S., M.H.A.,* LUIS DOMINGUEZ PARRA, M.D.,|| SYLVIA D. RODRIGUES, M.D.,# ROBERT J. LONG, M.D.,** AND MARGARET B. WALKER, M.D.††

*Baromedical Research Foundation, Columbia, SC; †Department of Radiation Oncology, Instituto Nacional de Cancerologia, Mexico City, Mexico; ‡Department of Epidemiology and Biostatistics, University of South Carolina Arnold School of Public Health, Columbia, SC; §Department of Underwater and Hyperbaric Medicine, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey; ¶Department of Family and Preventive Medicine, University of South Carolina School of Medicine, Columbia, SC; ||Department of Surgery, Instituto Nacional de Cancerologia, Mexico City, Mexico; #Department of Radiation Oncology, University of Pretoria Medical Centre, Pretoria, Republic of South Africa; **Wesley Centre for Hyperbaric Medicine, Wesley Medical Centre, Brisbane, Australia; and ††Department of Diving and Hyperbaric Medicine, Royal Hobart Hospital, Tasmania, Australia

Purpose: Cancer patients who undergo radiotherapy remain at life-long risk of radiation-induced injury to normal tissues. We conducted a randomized, controlled, double-blind crossover trial with long-term follow-up to evaluate the effectiveness of hyperbaric oxygen for refractory radiation proctitis.

Methods and Materials: Patients with refractory radiation proctitis were randomized to hyperbaric oxygen at 2.0 atmospheres absolute (Group 1) or air at 1.1 atmospheres absolute (Group 2). The sham patients were subsequently crossed to Group 1. All patients were re-evaluated by an investigator who was unaware of the treatment allocation at 3 and 6 months and Years 1–5. The primary outcome measures were the late effects normal tissue-subjective, objective, management, analytic (SOMA-LENT) score and standardized clinical assessment. The secondary outcome was the change in quality of life.

Results: Of 226 patients assessed, 150 were entered in the study and 120 were evaluable. After the initial allocation, the mean SOMA-LENT score improved in both groups. For Group 1, the mean was lower ($p = 0.0150$) and the amount of improvement nearly twice as great (5.00 vs. 2.61, $p = 0.0019$). Similarly, Group 1 had a greater portion of responders per clinical assessment than did Group 2 (88.9% vs. 62.5%, respectively; $p = 00009$). Significance improved when the data were analyzed from an intention to treat perspective ($p = 0.0006$). Group 1 had a better result in the quality of life bowel bother subscale. These differences were abolished after the crossover.

Conclusion: Hyperbaric oxygen therapy significantly improved the healing responses in patients with refractory radiation proctitis, generating an absolute risk reduction of 32% (number needed to treat of 3) between the groups after the initial allocation. Other medical management requirements were discontinued, and advanced interventions were largely avoided. Enhanced bowel-specific quality of life resulted.

Hyperbaric oxygenation, Controlled trial, SOMA-LENT, Late radiation injury, Quality of life.

Reprint requests to: Richard E. Clarke, C.H.T., 5 Richland Medical Park, Columbia, SC 29203. Tel: (803) 434-7101; Fax: (803) 434-4354; E-mail: dick.clarke@palmettohealth.org

Supported in part by grants from the Lotte and John Hecht Memorial Foundation and National Baromedical Services, and equipment from Sechrist Industries.

Supplementary material (Table 3) for this article can be found at www.redjournal.org.

Presented in part at the Undersea and Hyperbaric Medical Society Annual Scientific Meeting, Sydney, Australia, May 27–30, 2004; the Hyperbaric Nurses and Technicians Association Annual Meeting, Adelaide, Australia, August 9–11, 2007; and the Undersea and Hyperbaric Medical Society Gulf Coast Chapter Annual Scientific Meeting, Nashville, Tennessee. September 1, 2007.

Conflict of interest: R. E. Clarke provides hyperbaric medicine support services; and S. D. Rodrigues was compensated for lectures by Roche in 2007 and sat on the pain management board of Jansen Cilag in 2006.

Acknowledgments—We express our appreciation to Ms. Brandy Ayers for her preparation of the manuscript, to Ms. Stacy Handley for her editorial assistance, to Drs. Maide Cimsit, Samil Aktas, Adela Poitivin, and Jenny Wilson, who, in their capacity as department heads, encouraged and facilitated respective faculty members to participate as principal investigators, to Drs. Christopher LeRoux and Frans Cronje who made possible the Pretoria, Republic of South Africa collaboration, to Dr. Lindel Weaver for his provision of the patient blinding survey tool and his encouragement, to Dr. John Feldmeier for his comments regarding the study protocol, to Drs. John Yarnold and Roger Ahern for their review of the manuscript and helpful suggestions, to the hyperbaric staff members at each participating institution for their enthusiastic support of the trial and their commitment to protocol compliance, and finally to the patients who agreed to serve a subjects to whom we are particularly grateful.

Received Oct 19, 2007, and in revised form Dec 7, 2007. Accepted for publication Dec 12, 2007.

INTRODUCTION

Radiotherapy is a major nonoperative treatment and commonly used in the management of a number of different malignancies. During the past decade, significant developments in the delivery of radiotherapy have improved the efficacy and tolerance (1). Despite such advances, adverse effects continue to complicate its use (2, 3). These effects are commonly categorized as either acute effects, representing those that occur during or soon after radiotherapy completion, or late effects that manifest many months to several years later.

Acute toxicity is usually mild, frequently self-limiting, and often responds to brief interruptions in radiotherapy (3–5). Severe acute effects can lead to later excluded ones from ''consequential'' effects (6). Late toxicity is largely a function of the total radiation dose and fraction size and tends to be dose limiting in curative settings (7, 8). The resulting injuries are frequently refractory to a wide range of therapeutic interventions, can proceed to surgical removal of damaged organs, and are the cause of some mortality (2, 3, 9).

Late radiation proctitis is a particularly difficult condition to treat and for patients to live with (10–13). The reported incidence varies from 4% to 22% (5, 14), yet because of a frequent lack of recognition and insufficient long-term follow-up, its true incidence is unknown (14, 15). No recommended standard treatment exists, and current management is often unsatisfactory (11, 16). This shortcoming is readily apparent given the large number of medical and surgical therapies in common use (Table 1).

Hyperbaric oxygen (HBO) therapy has been used in the treatment of pelvic radiation injuries for several decades (Table 2) and has been reported to be beneficial (16–18). It has not, however, been studied in a sufficiently rigorous manner to determine its precise therapeutic effect. We conducted a multicenter, randomized, controlled, double-blind trial with crossover and long-term follow-up to evaluate the effect of HBO therapy for patients whose radiation proctitis had proven refractory to other interventions.

Table 1. Late radiation proctitis treatment options (in alphabetical order)

5-ASA
Antidiarrheal agents
Argon laser
Cautery
Corticosteroids
Dilation and stenting
Elemental diet
Formalin
Heat probe
Hormonal therapy
Hyperbaric oxygen therapy
Iron supplementation
Low-residue, low-fat diet
Metronidazole
Nd:YAG laser
Pain control
Pentosan
Resection
Replacement transfusion
Short-chain fatty acids
Sucralfate
Surgical repair

Abbreviations: ASA = acetylsalicylic acid (aspirin); Nd:YAG = neodymium:yttrium-aluminium-garnet (laser) ($Nd:Y_3Al_5O_{12}$).

METHODS AND MATERIALS

Patients

Patients from the Instituto Nacional de Cancerologica, Mexico City, Mexico, the University of Pretoria Medical Centre, Pretoria, Republic of South Africa, Department of Underwater and Hyperbaric Medicine, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, Wesley Medical Centre, Brisbane, Australia, and the Royal Hobart Hospital, Tasmania, Australia were enrolled in the trial. Each participating center's institutional review board approved the study protocol. Referring physicians agreed to participate as blinded assessors. The trial registration numbers were NCT00134628 and ISRCTN85456814.

Patients were eligible for enrollment if they had undergone pelvic radiotherapy and had subsequently developed evidence of rectal late radiation tissue injury. The diagnosis had to have been present for $\geq$3 months and to not have responded sufficiently to other therapies. Eligibility screening confirmed the absence of unacceptable patient-specific risks to HBO therapy. All patients or their surrogate provided written informed consent before enrollment. On patient enrollment, the best supportive care was maintained.

Before beginning treatment, patients were evaluated with the late effects normal tissue-subjective, objective, management, analytic (SOMA-LENT) scale, an anatomic-specific morbidity scoring system (19). It provides an ascending order of severity of radiation-induced complications. It is particularly well suited to multicenter trials, because of its standardized application, reproducibility, and accuracy. A standardized clinical assessment was also included with both screening tools conducted by a physician unaware of the allocation. Patients also completed the Expanded Prostate Cancer Index Composite (20) quality of life (QOL) instrument at this time and at every other follow-up stage.

Randomization

Biostatisticians at the University of South Carolina generated the randomization sequence, which was uploaded into, and concealed within, the study database software. The patients were randomly assigned (1:1) to receive HBO or normobaric air, using a ''blocking'' process. The block size was four and was equally stratified with two of each treatment options (A or B). The randomization sequence became available to the unblinded local principal investigator only on irretrievable entry of each patient's demographic information, medical history, and clinical characteristics. Group 1 (active treatment) was randomized to receive 2.0 atmospheres absolute (ATA) oxygen. Group 2 (sham) patients were randomized to receive 1.1 ATA air.

Treatment procedure

Group 1 was treated with 100% oxygen at 2.0 ATA for 90 min, once daily, five times weekly. Group 2 were treated with 21% oxygen (normal air) at 1.1 ATA, once daily, five times weekly. For patient blinding purposes, Group 2 patients underwent a brief compression to 1.34 ATA at the beginning of each treatment. The chamber was then slowly decompressed from 1.34 to 1.1 ATA.

Table 2. Reported hyperbaric oxygen dosing and outcomes for radiation proctitis

		Hyperbaric treatment			
Investigator	Patients *(n)*	Pressure (ATA)	Time (min)	Treatment sessions *(n)**	Overall improvement (%)
Bouachour *et al.* (31), 1990	8	2.5	90	80 ± 10	75
Charneau *et al.* (28), 1991	1	2.5	?	80	Healed
Nakada *et al.* (35), 1993	1	2.0	90	30	Healed
Hamour *et al.* (36), 1996	1	2.5	90	49	Healed
Feldmeier *et al.* (37), 1996	7	2.4	90	3–50 (24)	57
Woo *et al.* (38), 1997	18	2.0	90	12–40	>50
Warren *et al.* (39), 1997	14	2.0–2.5	90–120	?	59
Ugheoke *et al.* (40), 1998	8	2.5	90	20–40 (28)	62.5
Carl *et al.* (41), 1998	2	2.4	90	38–40 (39)	50
Gouello *et al.* (42), 1999	36	2.5	90	Mean 67	56–65
Kitta *et al.* (43), 2000	4	2.0	60	30–60 (38)	75
Bem *et al.* (44), 2000	2	2.4	90	60	100
Roque *et al.* (45), 2001	6	2.5	90	20–60 (37)	85
Mayer *et al.* (46), 2001	7	2.2–2.4	60	20–60 (33)	85
Boyle *et al.* (47), 2002	19	2.0	120	27–80 (59)	68
Jones *et al.* (48), 2006	10	2.0–2.5	90	36–41 (40)	>70
Dall'Era *et al.* (49), 2006	27	2.4	90	29–60 (36)	48
Fink *et al.* (50), 2006	4	2.4	90	20–50 (33)	50
Girnius *et al.* (51), 2006	9	2.5	90	22–80 (58)	78
Nakabayashi *et al.* (52), 2006	1	2.4	90	40	Healed
Marshall *et al.* (53), 2007	65	2.36	90	30–60	25–73

Abbreviation: ATA = atmospheres absolute.
* Average number of treatment sessions in parentheses.

Group 2 patients remained for the sum of the time taken to treat the Group 1 patients. Reassessment, after 30 treatment sessions, was undertaken by the referring physician, who remained unaware of the allocation. Ten additional treatment sessions were provided to selected patients, depending on the individualized responses. Patients repeated their QOL survey and were screened to determine the effectiveness of the blinding process. Unblinding took place at this point.

Those who had been allocated to Group 1 were entered into follow-up, with repeat evaluations scheduled at intervals of 3 and 6 months and Years 1–5. For Group 2, all but 3 accepted crossover to the active treatment arm.

Data collection at inclusion

Once a patient was enrolled, their local principal investigator collected the following data: age and gender; comprehensive medical history; current medications and any history of tobacco use; cancer-related history, including tumor type, location, stage, and treatment; and late radiation proctitis signs and symptoms, including treatment sessions to date.

Statistical analysis

The primary outcome was a change in the SOMA-LENT (Fig. 1) score, a numeric variable measured at all periods. Four other numeric values were derived from a QOL survey completed by patients in conjunction with their clinical evaluations. From this survey, using the Expanded Prostate Cancer Index Composite Bowel Domain, the Bowel Function and Bowel Bother subscales were obtained. Also obtained were the physical and mental results using the SF-12 General Health Function Survey. The SOMA-LENT score was analyzed using a repeated measures model containing patient type, period, their interaction, and six covariates: gender, tobacco use, external beam radiotherapy and brachytherapy, interval between radiotherapy and symptoms, interval between symptoms and treatment, and country of residence.

A sixth, ordinal categorical outcome, was the clinical evaluation measured at all periods, except at initialization. The evaluations made immediately after completion of the initial treatment allocation and crossover were coded as healed, significant improvement, modest improvement, or no improvement. For the remaining periods, they were coded as healed, improved, unchanged, or recurrence. For analysis purposes, these evaluations were dichotomized. After the initial treatment allocation and crossover, healed, significant improvement, and modest improvement were collapsed into one category and no improvement and recurrence into the other. For the follow-up evaluations, healed and improved were collapsed into one category and no improvement and recurrence into the other. The outcomes were compared for the two patient types using Fisher's exact test and logistic regression analysis containing the same variables as the repeated measures model for SOMA-LENT. Additionally, a Jonckheere-Terpstra test for trend was used with the original calculations.

RESULTS

A total of 226 patients were assessed for eligibility. Of these 226 patients, 76 were excluded and 150 enrolled. Of the 150 patients, 120 completed the protocol (Fig. 2). At 1 year, 5 patients (4%) had died and 9 (8%) had been lost to follow-up.

Descriptive statistics

Data were available for 120 patients. The minimal follow-up period for all patients was 1 year (average, 2.09). Of the 120 patients, 106 (88.33%) were women, and 101 (84.17%)

SOMA LENT scoring system for radiation proctitis

RADIATION PROCTITIS EVAL. BY: PRINT NAME:_____ HORTIS IV
PT. NAME_____HORTIS I.D._____ SIGNATURE: _____ DATE: _____

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	SCORE
Subjective					
Tenesmus	Occasional urgency	Intermittent urgency	Persistent urgency	Refractory	____
Mucosal loss	Occasional	Intermittent	Persistent	Refractory	____
Sphincter control	Occasional	Intermittent	Persistent	Refractory	____
Stool frequency	2 - 4 per day	4 - 8 per day	> 8 per day	Uncontrolled diarrhea	____
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	____
Objective					
Bleeding	Occult	Occasionally >2/week	Persistent/daily	Gross hemorrhage	____
Ulceration	Superficial ≤ 1 cm^2	Superficial > 1 cm^2	Deep ulcer	Perforation, Fistulae	____
Stricture	> 2/3 normal diameter with dilation	1/3 - 2/3 normal diameter with dilation	< 1/3 normal diameter	Complete obstruction	____
Management					
Tenesmus & stool frequency	Occasional, ≤ 2 antidiarrheals/week	Regular, > 2 antidiarrheals/week	Multiple, > 2 antidiarrheals/day	Surgical intervention/ Permanent colostomy	____
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	____
Bleeding	Stool softener, iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention / Permanent colostomy	____
Ulceration	Diet modification, stool softener	Occasional steroids	Steroids per enema, hyperbaric oxygen	Surgical intervention / Permanent colostomy	____
Stricture	Diet modification	Occasional dilatation	Regular dilatation	Surgical intervention	____
Sphincter control	Occasional use of incontinence pads	Intermittent use of incontinence pads	Persistent use of incontinence pads	Surgical intervention / Permanent colostomy	____

FACILITY CODE: _____

Scoring Instructions:

Score the 14 SOM parameters with 1-4 and total all 14 to generate the 1st LENT Score

(Score = 0 if there are no toxicities)

1st LENT Score_____

Divide the 1st LENT Score by 14 to provide the 2nd LENT Score

2nd LENT Score_____

Analytic		
Barium enema	Assessment of lumen and peristalsis	Y/N Date:
Proctoscopy	Assessment of lumen and musosal surface	Y/N Date:
CT	Assessment of wall thickness, sinus and fistula formation	Y/N Date:
MRI	Assessment of wall thickness, sinus and fistula formation	Y/N Date:
Anal manometry	Assessment rectal compliance	Y/N Date:
Ultrasound	Assessment of wall thickness, sinus and fistula formation	Y/N Date:

Fig. 1. Late effects normal tissue-subjective, objective, management, analytic (SOMA-LENT) scoring system for radiation proctitis.

reported never having smoked. Because of the small number of current ($n = 8$) and former ($n = 11$) smokers, the tobacco variable was dichotomized into ever/never. Of the 120 patients, 11 (9.17%) were from Australia, 85 (70.83%) from Mexico, and 12 (10.00%) from both South Africa and Turkey. The baseline comparisons of the covariates for the two groups resulted in no significant differences, indicating that the randomization process had worked well. The patient demographics and clinical characteristics are detailed in Table 3 (appears online only at www.redjournal.org). The mean SOMA-LENT values for the two patient types at each period are displayed in Fig. 3. The mean SOMA-LENT score decreased considerably between the initial value and completion of HBO therapy in Group 1, with a much smaller change in Group 2. For the latter group, however, a substantial decrease occurred after crossover, when they received HBO therapy.

Numeric outcomes

SOMA-LENT score. Adjusting for covariates, a significant ($p < 0.0001$) decrease (improvement) occurred in Group 1 of 5.00 (95% confidence interval, 3.96–6.03), as well as a significant ($p < 0.0001$) decrease in Group 2 of 2.61 (95% confidence interval, 1.51–3.70) after completion of the initial allocation. The decrease was greater in Group 1 than in Group 2 ($p = 0.0019$). At initialization, no difference was detected between the two groups ($p = 0.5597$). However, after the initial allocation, Group 1 had significantly ($p = 0.0150$) lower average scores than Group 2, with an estimated difference of 1.93 (95% confidence interval, 0.38–3.48). After completion of the crossover, no differences were detected ($p = 0.6594$). The mean scores remained relatively stable through 1 year and showed a trend to additional and sustained improvement through Year 5.

Clinical evaluation. The frequencies for clinical evaluations are given in Table 4. The most notable result was after completion of the initial allocation, at which 56 (88.9%) of the 63 patients in Group 1 were assessed to have either healed or had some improvement, and 32 (62.5%) of the 56 patients in Group 2 were assessed to have had at least some improvement. Fisher's exact test ($p = 0.0009$) and logistic regression

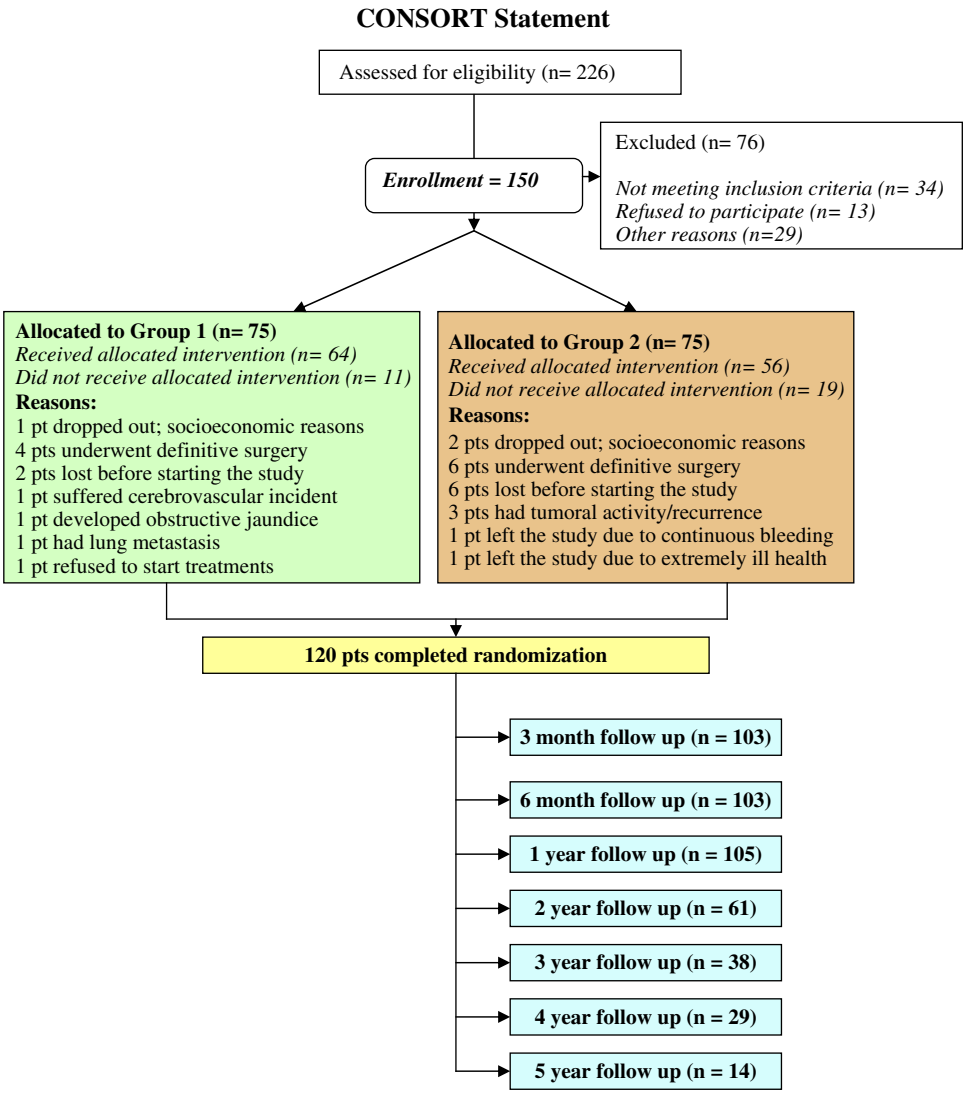

Fig. 2. Consolidated Standards of Reporting Trials (CONSORT) statement.

analysis ($p = 0.0011$) both indicated that Group 1 had a significantly greater proportion of healing/improvement at that time. For logistic regression analysis, the corresponding odds ratio was 5.93 (95% confidence interval 2.04–17.24). From this, we estimated that Group 1 was about six times more likely to have an evaluation that indicated at least some type of improvement than was Group 2. Furthermore, the Jonckheere-Terpstra test for trend was significant ($p = 0.0008$), indicating that better outcomes were more common in Group 1. On the basis of the clinical evaluation outcomes, an absolute risk reduction of 0.32 (32%) was generated, resulting in a number needed to treat of 3.

From an intention to treat perspective, we considered what would have happened if *(1)* all those for whom we had no results had had improvement, *(2)* all those for whom we had no results had not had improvement, and *(3)* for each patient type, one-half of those for whom we had no results had improvement and one-half had not. In all cases, the results still indicated that Group 1 had a significantly greater proportion of improvement than did Group 2 ($p = 0.0057$, $p = 0.0007$, and $p = 0.0036$, respectively).

Quality of life. Marked improvement was noted in the bowel-specific QOL assessment for Group 1 after treatment but not for Group 2 (14% for Bowel Bother and 9% for Bowel Function vs. 5% and 6%, respectively). After crossover, Group 2 showed notable improvement, with an increase to 13.6 for bowel bother and 10% for bowel function. Both groups showed additional improvement at 1 year. For the bowel bother subscale, a significant improvement was seen between initialization and randomization in Group 1 (estimated change, 14.14; $p = 0.0007$, adjusting for covariates), but not in Group 2 (estimated change, 5.75; $p = 0.1521$). However, Group 2 experienced a significant improvement after crossover (estimated change, 14.27; $p = 0.0002$). The scores for both groups were stable or tended to improve further throughout follow-up. Similar trends were seen in the bowel function subscale. No differences were observed in the general well-being assessment.

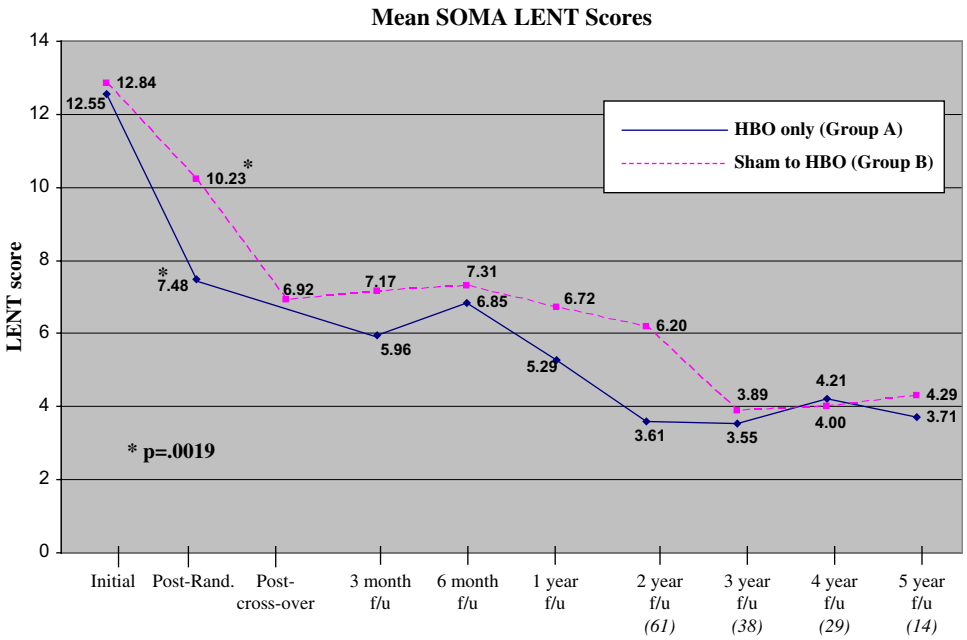

Fig. 3. Mean late effects normal tissue-subjective, objective, management, analytic (SOMA-LENT) scores. HBO = hyperbaric oxygen.

Patient beliefs

Of the 120 patients, 72 (33 in Group 1 and 39 in Group 2) were surveyed to determine which randomization allocation they had received. In Group 1, 20 said ''HBO,'' 1 said ''sham,'' and 12 ''could not say.'' In Group 2, these numbers were 23, 2, and 14. A chi-square test detected no relationship ($p = 0.9058$) between the patient opinions and what they had actually received. When patients who ''could not say'' were ignored, a Kappa statistic was $p = 0.0299$, indicating essentially no agreement beyond chance.

Harms

Consistent with hyperbaric practice, ear pain/ear discomfort (ear barotrauma) was the most common complaint. Ear barotrauma represents the clinical manifestation of an imbalance of pressure between the external and middle ear spaces. It is usually limited to the tympanic membrane, occasionally involves the middle ear, and only rarely involves the inner ear. Nineteen patients (15.8%) complained of ear pain or discomfort. The otologic examination was unremarkable in 11, 7 had tympanic membrane changes consistent with barotrauma, and 1 had both tympanic membrane injury and middle ear effusion. Decongestants were effective in 8 patients, 7 underwent ventilation tube placement, and 4 did not require treatment. One patient (0.8%) complained of sinus barotrauma and was successfully treated with decongestants.

Four patients (3.3%) experienced transient myopia. This is a poorly understood process and although thought to represent an oxidative stress-induced temporary alteration in the shape of the lens (21), its exact mechanism remains obscure.

Two patients (1.7%) complained of confinement anxiety. One was treated with reassurance alone; the other required mild sedation. No cases of acute central nervous system oxygen toxicity occurred. None of these harms compromised a patient's participation in the study, and all patients completed their prescribed treatment course.

DISCUSSION

Radiation proctitis is a common unfortunate complication of pelvic radiotherapy (22). Its reported incidence ranges from 4% to 22% (5, 7, 14) and can reach 36% after combination external beam radiotherapy and brachytherapy (23). More severe forms, some of which are life-threatening, have been reported to range from 4.3% to 22% (14, 24) with resulting mortality rates of 2–8% (3, 7, 24).

Most late cases occur within 3 years of radiotherapy completion, although latencies in excess of 10 years are not uncommon (14, 22). The natural history of late radiation proctitis is unpredictable. Minor symptoms can resolve either spontaneously (4) or with conservative management (2, 25). Other seemingly minor symptoms will prove refractory to standard care, resulting in disease progression despite increasingly aggressive interventions (24), and new forms of this complication can evolve (22). Minor complaints of pain and bleeding, therefore, cannot be characterized as harmless manifestations. Serious manifestations can necessitate high-risk surgery; high risk because tissues within the operative site might have been rendered hypoxic and poorly able to support oxygen-dependent wound repair. Ultimately, and having survived cancer, some patients will die of these complications (3, 7, 24).

The clinical presentation can involve any combination of tenesmus, urgency, diarrhea, constipation, sphincter dysfunction, mucoid or bloody discharge per rectum, frank bleeding, and ulceration, which can be localized, diffuse, or full thickness. The mucosa can appear granular, friable, edematous, and pale, with prominent submucosal telangiectatic

Table 4. Frequencies of clinical evaluations by patient type

Evaluation point	Clinical evaluation findings	Group 1	Group 2
Randomization*	Healed	5	0
	Significant improvement	24	15
	Moderate improvement	27	20
	No improvement	7	21
Crossover	Healed	1	3
	Significant improvement	0	33
	Moderate improvement	1	11
	No improvement	1	6
3-mo	Healed	5	2
	Improved	31	26
	Unchanged	18	18
	Cancer recurrence	1	2
6-mo	Healed	4	3
	Improved	30	24
	Unchanged	19	17
	Cancer recurrence	2	4
1-y	Healed	5	2
	Improved	32	30
	Unchanged	17	16
	Cancer recurrence	1	2
2-y	Healed	6	1
	Improved	21	12
	Unchanged	8	11
	Cancer recurrence	1	1
3-y	Healed	2	3
	Improved	15	12
	Unchanged	3	3
	Cancer recurrence	0	0
4-y	Healed	2	2
	Improved	12	10
	Unchanged	0	3
	Cancer recurrence	0	0
5-y	Healed	1	0
	Improved	4	6
	Unchanged	1	0
	Cancer recurrence	0	1

* p Values comparing groups after randomization were 0.0009 for Fisher's exact test, 0.0011 for logistic regression analysis, and 0.0008 for Jonckheere-Terpstra test for trend.

vasculature. Pain is common, ranging from occasional and minimal to refractory and excruciating.

The histologic findings can include microvascular compromise, endothelial cell degeneration, and formation of fibrin plugs (26). Submucosal fibrosis and obliteration of small blood vessels is additional evidence of late radiation injury. This process is usually progressive and irreversible. Computed tomography can demonstrate wall thickening, edema, ulcers, stricture, and fistula (27).

The medical treatment is not well defined and, in the absence of recommendations, management is often unsatisfactory (3, 8, 12, 22). One should do everything possible to avoid disease progression, however, because abdominopelvic operations (unavailable in the presence of perforation, obstruction, and fistula) within or through irradiated tissues are fraught with complications (8, 28).

High failure rates with conventional treatment led to the use of HBO therapy. Its beneficial effect, involving mandibular osteoradionecrosis, was first reported in 1973 (29). Resulting pathologic evidence of a progressive and obliterative endarteritis in mandibular osteoradionecrosis contrasted sharply with earlier assumptions of an osteomyelitic-like process (30). The finding that HBO therapy induced angiogenesis, suggested a disease-modifying mechanism, in contrast to more conventional medical and surgical therapies directed at relief of symptoms (16, 17).

Hyperbaric oxygen therapy was first reported to have efficacy in the treatment of late radiation proctitis in 1990 (31). Since then, numerous studies have been published (Table 2). In most instances, they represented small series or single case reports, did not use a specified toxicity scale, and lacked sufficient follow-up. However, the results from this accumulated work do suggest that HBO therapy is likely to be beneficial (16, 18).

We used SOMA-LENT scoring as a primary outcome measure. This numeric evaluation of radiation morbidity is simple, widely applicable, reproducible, and provides an ascending order of severity (19). Given that several different physicians would evaluate outcomes in this multicenter study, such uniform scoring was considered essential. The radiation proctitis SOMA-LENT process scores symptoms on a severity scale of 1–4 for each of five possible symptoms and three related objective clinical signs. Six management options, scored in increasing complexity, represent the final scoring element. The analytic measures used during the diagnostic workup can be recorded but are not scored.

Often, the outcome assessment is a function of clinical impression alone. This, however, opens evaluations to differences in interpretation and has the potential for bias. We elected to include this approach as a second primary outcome measure. Perhaps not surprisingly, the resulting percentage of clinical assessments determined as healed was lower than those reported in several previous studies. The specificity of the SOMA-LENT scale is such that an excellent healing response does not always result in a score of 0 (healed). A final response score of 2–3 might reflect a patient who, on presentation had a score of 15 for ulceration, intense pain, and persistent bleeding, required treatment with narcotics, occasional transfusions, and steroids, and whose post-treatment status became one of diet modification, twice-daily stool frequency, and an occasional non-narcotic analgesic. The clinical impression of this case would be one of ''healed'' by many. In the present trial, however, the clinical assessor also conducted each SOMA-LENT analysis. Recognizing that the score was not 0, the assessor might have been inclined to categorize the clinical outcome as something less than healed (*e.g.,* significantly improved).

The effect of HBO therapy, scored through the SOMA-LENT process, throughout the 5-year study period is shown in Fig. 3. Although the number of patients at Years 2–5 was 58%, 36%, 27%, and 13% of those at Year 1, respectively, a clear trend was seen toward continued and enduring healing.

A patient's perception of how effective a particular treatment is now represents one important element of the modern application of evidence-based medicine (32). The QOL effect of eliminating pain, minimizing hemorrhage, and normalizing stool frequency is obviously important. This effect was

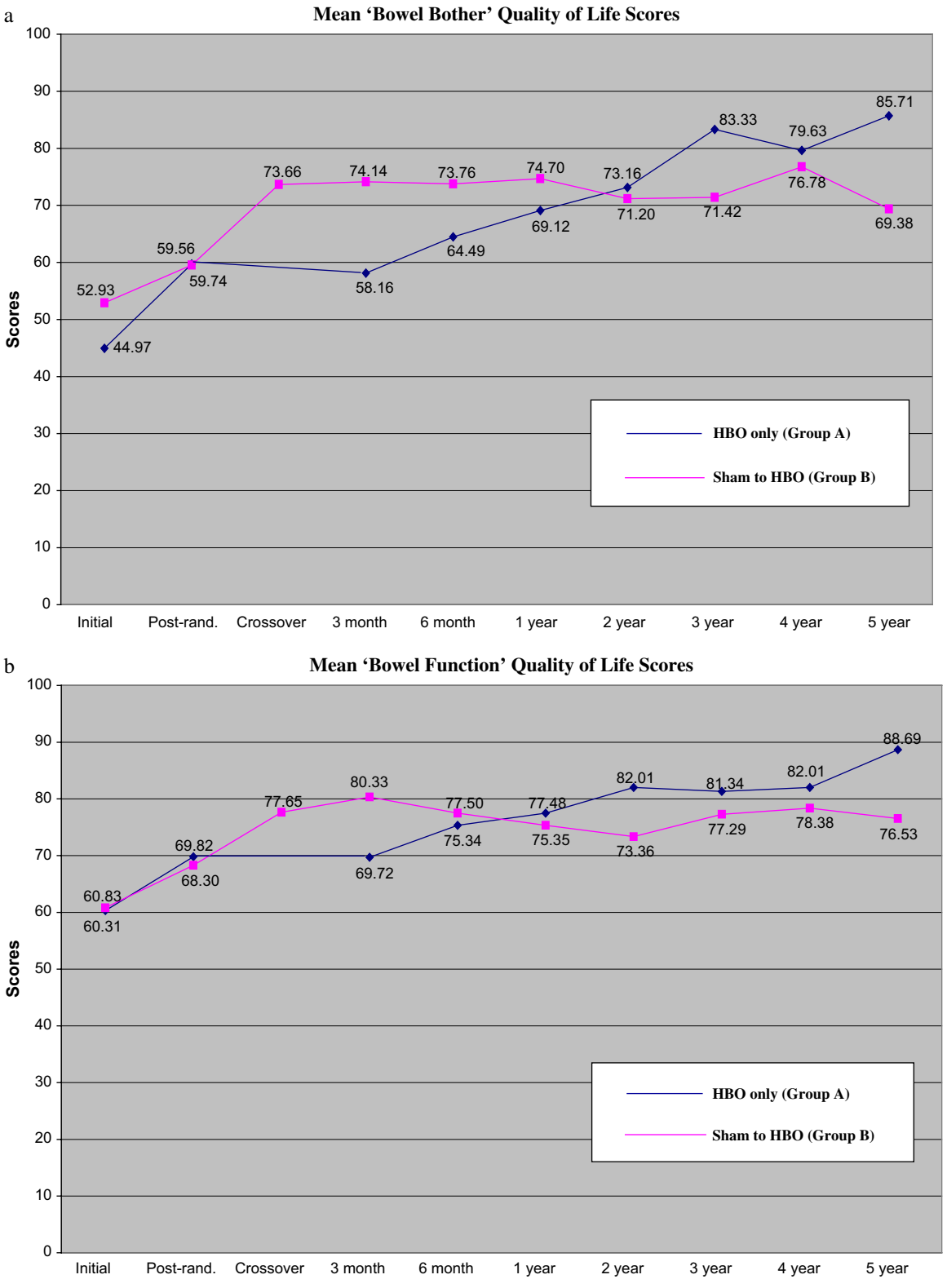

Fig. 4. (a) Bowel bother and (b) bowel function quality of life scores. HBO = hyperbaric oxygen.

evidenced by a significant improvement in the QOL recorded after receipt of HBO therapy in each group. The values continued to improve in Group 1 throughout the 5-year study period for bowel bother and bowel function. In Group 2, bowel bother continued to improve, and bowl function stabilized at its 1 year value throughout the remainder of the study (Fig. 4).

One final observation of some importance was an association between failure to respond and a finding of local recurrence or residual tumor. Three patients were diagnosed

with recurrence during the treatment phase. Eleven others were diagnosed during follow-up, for a recurrence rate of 11.7%. The SOMA-LENT scores in these patients had either remained elevated or improved, only to acutely deteriorate, by an average of 9 points (range, 4–17), by the time the recurrence was diagnosed.

In our study, approximately 45% of those patients without a treatment response were diagnosed with local recurrence. This finding argues for a measured approach to hyperbaric dosing. Ordering an initial hyperbaric course of more than 40 sessions is inadvisable. If little or no subsequent improvement occurs, workup for cancer recurrence should occur before any further hyperbaric treatments.

Hyperbaric oxygen therapy was well tolerated and its safety profile proved encouraging. These findings are consistent with standard practice, with hyperbaric medicine considered low risk. Predictably, no cases of oxygen toxicity developed. This was one of our study's safety goals, with the resulting treatment pressure selection of 2.0 ATA.

A patient's perception of how well, or otherwise, a specific therapy effects their daily living and overall QOL has only recently been recognized as an important outcome measure (32). In our study, patients considered HBO therapy to have an important positive effect on their QOL when measured against their primary complaint.

When numerous therapeutic options exist for a given condition, responsible resource expenditure assumes increasing importance. Although hyperbaric medicine's costs are not insignificant, its employment has resulted in an overall lowering of a patient's total healthcare financial burden (33, 34). Much of this cost reduction is achieved by avoiding repeated hospitalizations and surgeries, because greater disease resolution rates are effected. Such savings support a preference for disease-modifying interventions rather than those directed at relief of symptoms. The immediate and enduring effect of HBO therapy on the resolution or reduction in the degree of radiation proctitis would be expected to have a corresponding positive effect on the overall cost of care. Although we did not incorporate an economic analysis in this trial, several assumptions can be made. First, because disease progression is not uncommon (2, 9), avoiding it would be expected to result in a corresponding decrease in the healthcare costs necessary to manage advancing degrees of morbidity and the costs associated with management failure. Second, a reduction in disease severity, or its resolution, likewise would reduce the subsequent costs. Using the example of the mean improvement in SOMA-LENT change at 1 year in our trial, an index patient's requirements would change from repeated rectal examinations, regularly administered narcotics, multiple daily antidiarrheal agents and steroid enemas to occasional antidiarrheal agents, diet modification, and perhaps a stool softener. The financial implications related to this change in medical management are readily calculable.

CONCLUSION

The results of our study have shown that the provision of HBO therapy for patients with chronic refractory radiation proctitis resulted in significantly improved and enduring healing responses and enhanced QOL. Our results support the role of HBO therapy for soft-tissue radionecrosis.

REFERENCES

1. Duenas-Gonzalez A, Cetina L, Mariscal I, *et al*. Modern management of locally advanced cervical carcinoma. *Cancer Treat Rev* 2003;29:389–399.
2. O'Brien PC. Radiation injury of the rectum. *Radiother Oncol* 2001;60:1–4.
3. Johnston MJ, Robertson GM, Frizelle FA. Management of late complications of pelvic radiation in the rectum and anus. *Dis Colon Rectum* 2003;46:247–259.
4. O'Brien PC, Hamilton CS, Denham JW, *et al*. Spontaneous improvement in late rectal mucosal changes after radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58:75–80.
5. Chun M, Kang S, Kil HJ, *et al*. Rectal bleeding and its management after irradiation for uterine cervical cancer. *Int J Radiat Oncol Biol Phys* 2004;58:98–105.
6. Wang CJ, Leung SW, Chen HC, *et al*. The correlation of acute toxicity and late rectal injury in radiotherapy for cervical carcinoma: Evidence suggestive of consequential late effect (CQLE). *Int J Radiat Oncol Biol Phys* 1998;40:85–91.
7. Hamberger AD, Unal A, Gershenson DM, *et al*. Analysis of the severe complications of irradiation of carcinoma of the cervix: Whole pelvis irradiation and intracavitary radium. *Int J Radiat Oncol Biol Phys* 1983;9:367–371.
8. Gilinsky NH, Burns DG, Barbezat GO, *et al*. The natural history of radiation-induced proctosigmoiditis: An analysis of 88 patients. *Q J Med New Series LII* 1983;205:40–53.
9. Fischer L, Kimose HH, Spjeldnaes N, *et al*. Late progress of radiation-induced proctitis. *Acta Chir Scand* 1990;156:801–805.
10. Dent OF, Galt E, Chapuis PH, *et al*. Quality of life in patients undergoing treatment for chronic radiation-induced rectal bleeding. *Br J Surg* 1998;85:1251–1254.
11. Gammi B, Harrington K, Blake P, *et al*. How patients manage gastrointestinal symptoms after pelvic radiotherapy. *Aliment Pharmacol Ther* 2003;18:987–994.
12. Allen-Mersh TG, Wilson EJ, Hope-Stone HF, *et al*. The management of late radiation-induced rectal injury after treatment of carcinoma of the uterus. *Surg Gynecol Obstet* 1987;164:521–524.
13. Andreyev J. Gastrointestinal complications of pelvic radiotherapy: Are they of any importance? *Gut* 2005;54:1051–1054.
14. Eifel PJ, Levenback C, Wharton JT, *et al*. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1995;32:1289–1300.
15. Denton AS, Andreyev HJN, Forbes A, *et al*. Systematic review for non-surgical interventions for the management of late radiation proctitis. *Br J Cancer* 2002;87:134–143.
16. Feldmeier JJ, Hampson NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: An evidence based approach. *Undersea Hyperb Med* 2002;29:4–30.
17. Marx RE. A new concept in the treatment of osteoradionecrosis. *J Oral Maxillofac Surg* 1983;41:351–357.
18. Bennett MH, Feldmeier J, Hampson N, *et al*. Hyperbaric oxygen therapy for late radiation tissue injury (Protocol). The

Cochrane Database of Systematic Reviews 2004. Issue 2, Article No. CD005005.
19. Rubin P, Constine LS, Fajardo LF, *et al*. Overview: Late effects of normal tissues (LENT) scoring system. *Int J Radiat Oncol Biol Phys* 1995;31:1041–1042.
20. Wei J, Dunn R, Litwin M, *et al*. Development and validation of the Expanded Prostate Cancer Index Composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology* 2000;56:899–905.
21. Anderson B, Shelton DL. Axial length in hyperoxic myopia. Presented at the Ninth International Symposium on Underwater and Hyperbaric Physiology Undersea and Hyperbaric Medical Society, Bethesda, MD, 1987. p. 607–611.
22. Hong JJ, Park W, Ehrenpreis ED. Review article: Current therapeutic options for radiation proctopathy. *Aliment Pharmacol Ther* 2001;15:1253–1262.
23. Albert M, Tempany CM, Schultz D, *et al*. Late genitourinary and gastrointestinal toxicity after magnetic resonance image-guided prostate brachytherapy with or without neoadjuvant external beam radiation therapy. *Cancer* 2003;98:949–954.
24. Chapuis P, Dent O, Bokey E, *et al*. The development of a treatment protocol for patients with chronic radiation-induced rectal bleeding. *Aust NZ J Surg* 1996;66:680–685.
25. Zimmermann FB, Feldmann HJ. Clinical and pathological manifestations: Therapy and prophylaxis of acute and late injurious effects of radiation on the rectal mucosa. *Strahlenther Onkol* 1998;174(Suppl. III):85–89.
26. Carr ND, Pullen BR, Hasleton PS, *et al*. Microvascular studies in human radiation bowel disease. *Gut* 1984;25:448–454.
27. Capps GW, Fulcher AS, Szucs RA, *et al*. Imaging features of radiation-induced changes in the abdomen. *Radiographics* 1997;17:1455–1473.
28. Charneau J, Bouachour G, Person B, *et al*. Severe hemorrhagic radiation proctitis advancing to gradual cessation with hyperbaric oxygen. *Dig Dis Sci* 1991;36:373–375.
29. Mainous EG, Boyne PJ, Hart GB. Hyperbaric oxygen treatment of mandibular osteomyelitis: Report of three cases. *JADA* 1973; 87:1426–1430.
30. Marx RE. Osteoradionecrosis: A new chapter of its pathophysiology. *J Oral Maxillofac Surg* 1983;41:283–288.
31. Bouachour G, Ronceray J, Bouali AB, et al. Hyperbaric oxygen in the treatment of radiation induced proctitis: A report on 8 cases. Proceedings of the Tenth International Congress on Hyperbaric Medicine, Amsterdam, 1990. p. 158–163.
32. Haynes RB, Devereaux PJ, Guyatt GH. Clinical expertise in the era of evidence-based medicine and patient choice (Editorial). *ACP J Club* 2002;136:A11.
33. Marx R. Radiation injury to tissue. In: Kindwall E, Whelan H, editors. Hyperbaric medicine practice. 2nd ed., revised. Flagstaff, AZ: Best Publishing; 2004. p. 665–723.
34. Dempsey J, Hynes N, Smith T, *et al*. Cost effectiveness analysis of hyperbaric therapy in osteoradionecrosis. *Can J Plast Surg* 1997;5:221–229.
35. Nakada T, Kubota Y, Sasagawa I, *et al*. Therapeutic experience of hyperbaric oxygenation in radiation colitis. *Dis Colon Rectum* 1993;36:962–965.
36. Hamour AA, Denning DW. Hyperbaric oxygen therapy in a woman who declined colostomy. *Lancet* 1996;348:197.
37. Feldmeier JJ, Heimbach RD, Davolt DA, *et al*. Hyperbaric oxygen an adjunctive treatment for delayed radiation injuries of the abdomen and pelvis. *Undersea Hyperbaric Med* 1996; 23:205–213.
38. Woo TCS, Joseph D, Oxer H. Hyperbaric oxygen treatment for radiation proctitis. *Int J Radiat Oncol Biol Phys* 1997;38: 619–622.
39. Warren DC, Feehan P, Slade JB, *et al*. Chronic radiation proctitis treated with hyperbaric oxygen. *Undersea Hyperb Med* 1997;24:181–184.
40. Ugheoke EA, Norris T, Sharma VK, et al. Radiation proctitis (RTP): Is there a role for hyperbaric oxygen (HBO) therapy? Proceedings of the American College of Gastroenterology 63rd Annual Scientific Meeting, October 12–14, 1998, Boston, MA.
41. Carl UM, Peusch-Dreyer D, Frieling T, *et al*. Treatment of radiation proctitis with hyperbaric oxygen: What is the optimal number of HBO treatments? *Strahlenther Onkol* 1998;174:482–483.
42. Gouello JP, Bouachour G, Person B, *et al*. The role of hyperbaric oxygen therapy in radiation-induced digestive disorders: 36 cases. *Presse Med* 1999;28:1053–1057.
43. Kitta T, Shinohara N, Shirato H, *et al*. The treatment of chronic radiation proctitis with hyperbaric oxygen in patients with prostate cancer. *BJU Int* 2000;85:372–374.
44. Bem J, Bem S, Singh A. Use of hyperbaric oxygen chamber in the management of radiation-related complications of the anorectal region. *Dis Colon Rectum* 2000;43:1435–1438.
45. Roque F, Saraiva A, Simao G, et al. Hyperbaric oxygen therapy for late radio-induced intestinal lesions. Proceedings of the European Society for Therapeutic Radiology and Consensus Conference, Lisbon, Portugal, 2001. p. 105–121.
46. Mayer R, Klemen H, Quehenberger F, *et al*. Hyperbaric oxygen—An effective tool to treat radiation morbidity in prostate cancer. *Radiother Oncol* 2001;61:151–156.
47. Boyle BR, Moon RE, Stolp BW, *et al*. Hyperbaric oxygen therapy for chronic radiation proctitis (CRP) [Abstract]. *Undersea Hyperb Med* 2002;29(Suppl.):19.
48. Jones K, Evans AW, Bristow RG, *et al*. Treatment of radiation proctitis with hyperbaric oxygen. *Radiother Oncol* 2006;78: 91–94.
49. Dall'Era MA, Hampson NB, His RA, *et al*. Hyperbaric oxygen therapy for radiation induced proctopathy in men treated for prostate cancer. *J Urol* 2006;176:87–90.
50. Fink D, Chetty N, Lehm JP, *et al*. Hyperbaric oxygen therapy for delayed radiation injuries in gynecological cancers. *Int J Gynecol Cancer* 2006;16:638–642.
51. Girnius S, Cersonsky N, Gesell L, *et al*. Treatment of refractory radiation-induced hemorrhagic proctitis with hyperbaric oxygen therapy. *Am J Clin Oncol* 2006;29:588–592.
52. Nakabayashi M, Beard C, Kelly SM, *et al*. Treatment of a radiation-induced rectal ulcer with hyperbaric oxygen therapy in a man with prostate cancer. *Urol Oncol Semin Orig Invest* 2006;24:503–508.
53. Marshall GT, Thirlby RC, Bredfeldt JE, *et al*. Treatment of gastrointestinal radiation injury with hyperbaric oxygen. *Undersea Hyperb Med* 2007;34:35–42.

APPENDIX

The clinical evaluation team included Dr. Fulya Yaman Agaoglu, Dr. Ridvan Avul, Dr. Robyn Cheuk, Dr. Yavuz Dizdar, Dr. Aaron Gonzalez, Dr. Susan Houldsworth, Dr. Esra Kaytan, Dr. Everine Klopper, Mr. Robert Lincacre, Dr. James Mackean, Dr. Robbie de Meulenare, Dr. Aida Mota, Dr. Gonzalo Montalvo, Dr. Browwyn Mueller, Dr. Binnur Pinarbasi, Dr. Ken Purdie, Dr. Marlene Soares, Dr. John Stephenson, Dr. Colin Tang, Dr. Cherian Varughese, Dr. Albert Verbeek, Dr. Margaret Wallington, and Dr. Alida Wolvaardt. The study monitors included Ms. Guillermina Silva, Lic.Enf., Dr. Baris Pekicten, Mr. Stephen Goble, and Ms. Surita Fitchat, R.N.

Table 3. Patient demographics

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments			Time to LENT diagnosis (*mo*)*	LENT presentation	Previous LENT treatment†	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
					Surgery (type)	*Chemotherapy (type/dose)*	*RT/dosage*							
PROC 001B	F	3/16/1998	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,031.75 cGy	12	Diarrhea, hemorrhage, stricture	2, 5	Never	No	No	No
PROC 002B	F	2/26/1999	Uterine cervix	AC/IIb	*Hysterectomy + BSO*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,500 cGy	16	Hemorrhage	2	Never	No	No	No
PROC 003A	F	12/8/1999	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,689 cGy	12	Diarrhea, hemorrhage	2	Never	No	No	No
PROC 004A	F	11/26/1998	Uterine cervix	AC/Ib2	*Hysterectomy + BSO*	No	X-ray, 4,600 cGy (200 cGy x 23 fractions) Brachytherapy, 3,344 cGy	16	Diarrhea, hemorrhage	2	Never	No	No	No
PROC 005A	F	6/9/1999	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,961 cGy	13	Pain, hemorrhage	2	Never	No	No	No
PROC 006A	F	11/4/1999	Uterine cervix	SCC/IIa	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,695 cGy	13	Hemorrhage	2	Never	No	No	No
PROC 007B	F	2/11/2000	Uterine cervix	AC/IIb	*Extrafascial hysterectomy*	No	X-ray, 5,000 cGy (200 cGy x 16 + 300 cGy x 8) Brachytherapy, 2,571 cGy	10.5	Pain, hemorrhage, ulceration, stricture	2, 12 (Diet)	Never	No	No	Yes
PROC 008B	F	8/11/1995	Uterine cervix	SCC/Ib2	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,848 cGy	14	Hemorrhage	1, 2, 12 (Sucralfate)	Never	No	No	Yes
PROC 009A	F	8/24/1999	Uterine cervix	SCC/IIIb	No	*Cisplatin/ 250 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,841 cGy	6	Hemorrhage	2	Never	No	No	No

(*Continued*)

PROC 010B	F	12/17/1999	Uterine cervix	SCC/IIIb	No	*Cisplatin/ 360 mg*	X-ray, 5600 cGy (200 cGy x 28 fractions) Brachytherapy, 3,600 cGy	12	Hemorrhage	2	Never	No	No	No
PROC 011A	F	10/24/1994	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,653 cGy	13	Hemorrhage	2	Never	No	No	No
PROC 012B	F	12/1/1999	Uterine cervix	SCC/IIa	No	*Cisplatin/ 420 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,335 cGy	14	Hemorrhage, wall changes (fibrotic)	1				
PROC 013A	F	1/19/2000	Uterine cervix	SCC/IIb	No	No	X-ray, 4800 cGy (300 cGy x 16 fractions) Brachytherapy, 3,000 cGy	14	Hemorrhage	4	Never	No	Yes	No
PROC 014B	F	4/21/1998	Uterine cervix	SCC/Ib1	*Hysterectomy + BSO*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,885 cGy	35	Pain, hemorrhage, Unspecific chronic colitis	2, 12 (Diet, steroid enema)	Never	Yes	No	No
PROC 015A	F	4/13/2000	Uterine cervix	SCC/Ib2	*Radical hysterectomy and pelvic lymphadenectomy*	No	X-ray, 4,900 cGy (300 cGy x 7 fractions + 200 cGy x 14 fractions) Brachytherapy, 3,673 cGy	14	Diarrhea, pain, hemorrhage, stricture, mild chronic colitis	2	Never	No	No	Yes
PROC 016B	F	8/20/1998	Uterine cervix	SCC/Ib1	*Abdominal hysterectomy*	No	X-ray, 5,040 cGy (180 cGy x 28 fractions) Brachytherapy, 2,904 cGy	14.5	Hemorrhage, Chronic cystitis	11, 12 (Sucralfate and cystitis after RT with dimethyl sulfoxide)	Never	No	No	Yes
PROC 017B	F	11/8/1999	Uterine cervix	SCC/IIIb	No	*Cisplatin/ 360 mg*	X-ray, 6,520 cGy (200 cGy x 29 fractions + 180 cGy x 4 fractions) Brachytherapy, 2,031 cGy	19	Diarrhea, pain, hemorrhage, ulceration	2, 11, 12 (Steroids, Bicap)	Never	No	No	No
PROC 018B	F	6/29/2000	Uterine cervix	SCC/Ib2	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 4,329 cGy	11.5	Pain, hemorrhage, ulceration, Chronic mild colitis.	2	Never	No	No	No
PROC 019A	F	4/4/2000	Uterine cervix	SCC/Ib2	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 4,685 cGy	8	Diarrhea, hemorrhage, chronic ileocolitis, enteritis	2, 12 (Sucralfate)	Never	No	No	Yes

(*Continued*)

Table 3. Patient demographics (*continued*)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments			Time to LENT diagnosis (*mo*)*	LENT presentation	Previous LENT treatment†	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
					Surgery (type)	*Chemotherapy (type/dose)*	*RT/dosage*							
PROC 020A	F	10/1/1998	Uterine cervix	AC/IIb	*Complementary TAH*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,503 cGy	17.5	Hemorrhage	2, 11	Never	Yes	No	No
PROC 021A	F	7/21/1999	Uterine cervix	ASCC/IIIb	*Complementary TAH*	*Cisplatin/ 300 mg*	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 3,808 cGy	15.5	Hemorrhage	2	Current use	Yes	Yes	Yes
PROC 022B	F	9/8/1999	Uterine cervix	SCC/IIb	No	*Cisplatin/ 360 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,276 cGy	13	Hemorrhage	2	Never	No	No	No
PROC 023B	F	11/1/1999	Uterine cervix	SCC/IIb	No	No	X-ray, 4,600 cGy (200 cGy x 23 fractions) Brachytherapy, 6,696 cGy	17	Hemorrhage	2	Never	Yes	Yes	No
PROC 024A	F	4/23/1999	Uterine cervix	SCC/IIb	No	*Irinotecan/ 1,478 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,853 cGy	27	Diarrhea, hemorrhage	2, 5	Never	Yes	No	No
PROC 025A	F	3/16/2000	Uterine cervix	SCC/Ib2	No	No	X-ray, 4,599.9 cGy (242.1 cGy x 19 fractions) Brachytherapy, 3,239.5 cGy	17.5	Hemorrhage, ulceration	2	Current use	No	Yes	No
PROC 026A	F	6/12/2000	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,500 cGy	12	Hemorrhage, ulceration	2, 12 (Diet)	Never	No	No	No
PROC 027B	F	7/4/2000	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,729 cGy	10.5	Hemorrhage, ulceration	12 (Pentoxyphiline, tocopherol)	Past use	No	No	No
PROC 028B	F	7/3/2000	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,577 cGy	14.5	Pain	2	Never	No	No	No

(*Continued*)

PROC 029A	F	11/1/1999	Uterine cervix	SCC/Ib2	No	*Cisplatin/ 300 mg*	X-ray, 4,600 cGy (200 cGy x 23 fractions) Brachytherapy, 3300 cGy	4.5	Hemorrhage, ulceration, Concurrent cystitis	2	Never	Yes	No	Yes
PROC 030B	F	8/2/1999	Uterine cervix	SCC/Ib2	No	*Cisplatin/ 50 mg*	X-ray, 5,200 cGy (400 cGy x 3 + 200 cGy x 20 fractions) Brachytherapy, 3,500 cGy	21	Diarrhea, hemorrhage	2, 12 (Diet)	Never	No	No	No
PROC 031A	F	5/15/2000	Uterine cervix	SCC/IIb	No	No	X-ray, 4,800 cGy (300 cGy x 16 fractions) Brachytherapy, 3,500 cGy	15.5	Hemorrhage, ulceration	12 (Ferrous sulfate and diet)	Never	Yes	No	No
PROC 032B	F	7/24/2000	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,227 cGy	8	Hemorrhage, stricture	2, 12 (Diet and metronidazole)	Never	No	No	No
PROC 033A	F	6/29/2000	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,500 cGy	8	Diarrhea, pain, hemorrhage	2	Past use	Yes	Yes	No
PROC 034A	F	1/24/2000	Uterine cervix	SCC/IIb	No	*Cisplatin/ 360 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 4,352 cGy	10	Hemorrhage	11	Never	No	Yes	No
PROC 035B	F	5/2/2000	Uterine cervix	SCC/Ib2	No	No	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 3,119 cGy	13.5	Hemorrhage, ulceration, stricture	2, 11	Never	No	No	Yes
PROC 036B	F	11/11/1999	Uterine cervix	SCC/IIIb	No	*Cisplatin/ 360 mg*	X-ray, 5600 cGy (200 cGy x 28 fractions) Brachytherapy, 3,800 cGy	2.5	Hemorrhage	2	Never	No	No	No
PROC 037B	F	10/20/1999	Uterine cervix	SCC/IIIb	No	No	X-ray, 6,000 cGy (200 cGy x 30 fractions)	22	Hemorrhage	2	Current use	No	No	No
PROC 038B	F	4/14/2000	Uterine cervix	SCC/IIa	*TAH*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,928 cGy	14.5	Hemorrhage	2, 12 (Diet)	Never	No	No	Yes
PROC 039A	F	2/12/2001	Uterine cervix	ASCC/Ib2	*TAH*	No	X-ray, 5,000 cGy (200 cGy x 19 + 400 cGy x 3 fractions) Brachytherapy, 3,500 cGy	11	Hemorrhage, ulceration, stricture	12 (Ferrous Sulfate)	Never	No	No	No

(*Continued*)

Table 3. Patient demographics (*continued*)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments			Time to LENT diagnosis (*mo*)*	LENT presentation	Previous LENT treatment†	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
					Surgery (type)	*Chemotherapy (type/dose)*	*RT/dosage*							
PROC 040A	F	9/9/1999	Uterine cervix	SCC/IIb	No	No	X-ray, 5200 cGy (200 cGy x 20 + 400 cGy x 3 fractions) Brachytherapy, 3,792 cGy	14	Hemorrhage	2, 11	Never	No	No	Yes
PROC 041B	F	12/13/2000	Uterine cervix	SCC/IIIb	No	No	X-ray, 7,000 cGy (200 cGy x 35 fractions)	6	Pain, hemorrhage	2	Never	No	No	No
PROC 042B	F	8/25/1997	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,600 cGy (200 cGy x 28 fractions) Brachytherapy, 3,000 cGy	53.5	Hemorrhage, ulceration	2	Never	Yes	No	Yes
PROC 043A	F	2/28/2001	Uterine cervix	SCC/IIb	No	*Cisplatin/ 350 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2162 cGy	13.5	Hemorrhage	12 (Diet)	Past use	No	No	No
PROC 044A	F	2/28/2001	Uterine cervix	SCC/IIb	No	*Cisplatin/ 350 mg*	Brachytherapy, 3654 cGy	15.5	Hemorrhage	2	Past use	No	No	Yes
PROC 045B	F	10/29/1999	Uterine cervix	SCC/IIIb	No	No	X-ray, 6,600 cGy (200 cGy x 33 fractions) Brachytherapy, 3,500 cGy	44.5	Diarrhea, hemorrhage	2, 5	Past use	No	No	Yes
PROC 046A	F	7/23/2001	Uterine cervix	SCC/IIb	No	*Cisplatin/ 360 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2879 cGy	10.5	Diarrhea, pain, hemorrhage, ulceration, stricture	3	Past use	No	No	No
PROC 047A	F	4/18/2000	Uterine cervix	ASCC/Ib1	No	No	X-ray, 7,000 cGy (200 cGy x 25 + 200 cGy x 10 fractions)	26.5	Bleeding, metabolic disorder	12 (Diet)	Never	Yes	No	Yes
PROC 048B	M	10/7/2000	Prostate	AC	No	No	X-ray, 6,840 cGy (180 cGy x 38 fractions)	17	Diarrhea, pain, hemorrhage, fistula, edematous wall changes	2, 3	Current use	No	Yes	No
PROC 049A	F	6/1/2001	Uterine cervix	SCC/IIIb	No	*Cisplatin/ 200 mg*	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 3,704 cGy	13	Diarrhea, pain, hemorrhage, ulceration, stricture	2	Never	No	No	Yes

(*Continued*)

PROC 050B	F	6/23/1997	Uterine cervix	SCC/IIa	No	No	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 3,493 cGy	51.5	Hemorrhage	2, 12 (Diet)	Never	No	No	Yes
PROC 051B	F	4/30/2001	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,956 cGy	12.5	Pain, ulceration	1	Never	No	No	Yes
PROC 052A	F	5/7/2001	Uterine cervix	SCC/IIa	No	*Cisplatin/ 350 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,331 cGy	18.5	Diarrhea, pain, hemorrhage, ulceration	2	Past use	No	No	Yes
PROC 053B	F	4/14/2000	Uterine cervix	SCC/IIb	*TAH*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,670 cGy	20	Hemorrhage	2	Never	No	Yes	No
PROC 054A	F	12/3/2002	Uterine cervix	Cancer epidermoid/IIb	No	No	X-ray, 7600 cGy (200 cGy x 38 fractions) Brachytherapy, 2,486 cGy		Hematuria	12 (Diet)	Never	No	No	No
PROC 055A	F	3/14/2001	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,578 cGy	12	Hemorrhage	2	Never	No	No	No
PROC 056B	F	3/3/2000	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,100 cGy (300 cGy x 17 fractions) Brachytherapy, 3,400 cGy	16.5	Hemorrhage	1	Never	No	No	No
PROC 057A	F	9/3/1984	Uterine cervix	SCC/IIa	No	No	X-ray, 4,600 cGy (200 cGy x 23 fractions) Brachytherapy, 3,456 cGy	28	Hemorrhage	12 (Diet)	Never	No	No	No
PROC 058A	F	11/8/2000	Uterine cervix	SCC/Ib2	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,785 cGy	12.5	Hemorrhage	12 (Steroid use)	Never	No	No	Yes
PROC 059B	F	11/14/2000	Uterine cervix	SCC/Ib1	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,777 cGy	18	Hemorrhage	12 (Steroid use)	Never	No	Yes	Yes
PROC 060B	F	11/30/2000	Uterine cervix	SCC/IIIb	No	*Cisplatin/ 240 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,022 cGy	16.5	Cramping, pain, hemorrhage	2, 12 (Diet, steroid enema)	Never	No	No	No

(*Continued*)

Table 3. Patient demographics (*continued*)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments			Time to LENT diagnosis (*mo*)*	LENT presentation	Previous LENT treatment†	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
					Surgery (type)	*Chemotherapy (type/dose)*	*RT/dosage*							
PROC 061A	F	1/3/2001	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 4,238 cGy	16	Diarrhea, hemorrhage, cramping	2	Never	No	No	No
PROC 062B	F	11/26/1998	Uterine cervix	SCC/Ib2	No	No	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 3,562 cGy	10.5	Hemorrhage	2	Never	No	Yes	Yes
PROC 063A	F	12/13/2000	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,517 cGy	19.5	Hemorrhage	2	Never	No	No	Yes
PROC 064B	F	9/24/1999	Uterine cervix	SCC/IIb	No	*Cisplatin/ 420 mg*	X-ray, 5600 cGy (200 cGy x 28 fractions) Brachytherapy, 3,122 cGy	14	Diarrhea, pain, hemorrhage	2	Never	No	No	No
PROC 065A	F	11/6/2001	Uterine cervix	SCC/IIb	*Radical hysterectomy*	*Cisplatin/ 420 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions)	8.5	Hemorrhage, edematous wall change	2	Never	No	No	Yes
PROC 066A	M	5/1/2001	Prostate	AC	No	No	X-ray, 6840 cGy (180 cGy x 38 fractions)	19	Hemorrhage, ulceration, Wall changes (Mucosal thickening)	2	Current use	No	Yes	No
PROC 067B	F	7/16/2001	Uterine cervix	SCC/IIb	No	*Cisplatin/ 390 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,549 cGy	9	Pain, hemorrhage, ulceration, stricture	2	Never	No	No	No
PROC 068B	F	11/21/2001	Uterine cervix	SCC/IIIb	No	*Carboplatin/ 450 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,488 cGy	16	Hemorrhage, ulceration, edematous wall changes	2	Never	Yes	No	Yes
PROC 069A	F	12/11/2001	Uterine cervix	SCC/IIb	No	*Cisplatin/ 300 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,321 cGy	8.5	Diarrhea, hemorrhage	2	Never	No	Yes	Yes
PROC 070B	F	9/20/2002	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 4,027 cGy	13.5	Constipation, hemorrhage, ulceration	2	Never	No	Yes	No

(*Continued*)

PROC 071A	F	11/21/2001	Uterine cervix	SCC/IIb	No	*Cisplatin/ 350 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,209 cGy	13.5	Hemorrhage	2	Never	No	No	No
PROC 072B	F	6/20/2001	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,529.68 cGy	3.5	Hemorrhage	12 (Diet)	Never	Yes	No	Yes
PROC 073B	M	10/28/1998	Rectum	AC	*Low anterior resection + end-to-end anastomoses*	*FU (400 mg) + FA (20 mg)*	X-ray, 5040 cGy (180 cGy x 28 fractions)	44	Pain, hemorrhage, stricture, wall changes (edematous, fibrotic)	NA	Past use	No	Yes	No
PROC 074B	F	4/5/2002	Uterine cervix	Other (glassy cells)/IIb	*Hysterectomy + BSO*	*PVC (before RT, platinum 150 mg, after RT vincristine 400 mg 400 mg with platinum 40 mg)*	X-ray, 5,312 cGy (180 cGy x 29 fractions) Brachytherapy, 6,804 cGy	17.5	Hemorrhage	2	Never	No	No	No
PROC 075A	F	7/26/2000	Uterine cervix	SCC/IIb	No	*Cisplatin/300 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,085 cGy	16.5	Hemorrhage, ulceration, stricture	2, 12 (Dilatation)	Never	No	No	No
PROC 076A	F	4/18/2002	Uterine cervix	ASCC/IIIb	No	*Cisplatin/300 mg*	X-ray, 6,000 cGy (200 cGy x 30 fractions)	16	Hemorrhage	2	Never	No	No	Yes
PROC 077A	F	5/3/2002	Uterine corpus	AC	*TAH*	*Cisplatin/ 450 mg + Cyclophosphamide/ 4,500 mg*	X-ray, 5400 cGy (200 cGy x 27 fractions) Brachytherapy, 3,486 cGy	17.5	Constipation, hemorrhage ulceration	2, 12 (Metronidazole)	Never	No	No	No
PROC 078B	F	6/11/2000	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,781 cGy	9.5	Hemorrhage	2, 12 (Diet)	Never	No	No	Yes
PROC 079A	F	3/3/2003	Uterine cervix	SCC/IIIa	No	*Cisplatin/350 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,750 cGy	10	Diarrhea, Constipation, pain, Hemorrhage, wall changes (edematous, mucosal thickening), other (hyperemia, erosions)	2, 3, 5, 12 (Steroid enema)	Never	No	No	Yes
PROC 080B	F	5/20/2002	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,077 cGy	19	Hemorrhage	2, 12 (Steroid enema)	Never	No	No	No

(*Continued*)

Table 3. Patient demographics (*continued*)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments			Time to LENT diagnosis (*mo*)*	LENT presentation	Previous LENT treatment†	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
					Surgery (type)	*Chemotherapy (type/dose)*	*RT/dosage*							
PROC 081A	F	5/10/2001	Uterine corpus	AC	*Hydrothermal ablation*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,751 cGy	14	Hemorrhage	2	Never	No	No	No
PROC 082A	F	1/7/2002	Uterine corpus	AC	*TAH*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,462 cGy	22	Hemorrhage	2	Never	Yes	Yes	No
PROC 083B	F	9/2/2002	Uterine cervix	SCC/IIIb	No	*Gemzar/ 2700 mg*	X-ray, 5,600 cGy (200 cGy x 28 fractions) Brachytherapy, 2,132 cGy	11.5	Hemorrhage	2	Never	No	No	Yes
PROC 084B	F	2/15/2003	Uterine corpus	AC	*TAH*	No	X-ray, 5040 cGy (180 cGy x 28 fractions) Brachytherapy, 1,800 cGy	12.5	Cramping, constipation, pain, hemorrhage, ulceration, endarteritis, wall changes (edematous)	3, 12 (Coagulation by adrenaline injection and heater probe)	Never	No	No	Yes
PROC 085A	F	1/25/2002	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,817 cGy	19.5	Hemorrhage	2	Never	No	No	No
PROC 086B	F	1/21/2003	Uterine corpus	AC	*TAH + BSO, node sampling*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 5,000 cGy	10.5	Pain, hemorrhage, ulceration	NA	Never	No	No	Yes
PROC 087B	F	7/2/2002	Uterine corpus	AC	*TAH*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,775 cGy	8	Hemorrhage	2	Never	No	No	No
PROC 088A	F	7/5/2002	Uterine cervix	SCC/IIa	No	*Carboplatin/ 200 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,827 cGy	8.5	Hemorrhage	2	Never	Yes	Yes	Yes
PROC 089B	F	5/24/2002	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,153 cGy	19.5	Hemorrhage	2	Never	No	No	No

(*Continued*)

PROC 090A	F	5/20/2001	Uterine cervix	SCC/IIIa	*Cone biopsy*	*Cisplatin/390 mg*	X-ray, 5,500 cGy (183.33cGy x 30 fractions) Brachytherapy, 2,000 cGy	14	Cramping, pain, stricture, Perforation	12 (Diet)	Current use	No	No	No
PROC 091B	F	3/26/2001	Uterine cervix	SCC/IIIb	No	No	Co60 (pendulum), 6,750 cGy (250 cGy x 27 fractions)	29.5	Pain, hemorrhage, ulceration	5	Never	No	No	Yes
PROC 092A	M	3/28/2003	Prostate	AC	No	No	X-ray, 7,200 cGy (200 cGy x 36 fractions)	11	Pain, hemorrhage, ulceration	2, 5	Past use	No	Yes	No
PROC 093B	F	10/1/1990	Uterine corpus	Carcinosarcoma *(mixed malignant mullerian tumor)*	*TAH + BSO, lymphadenectomy*	*Cisplatin Adriamycin (dose unknown)*	X-ray, 4,500 cGy (1.8cGy x 25 fractions) Brachytherapy, 6,000 cGy	106	Diarrhea, vomiting, pain, Cramping, hemorrhage	3, 4, 5	Past use	No	No	No
PROC 094A	F	4/4/2003	Uterine cervix	SCC/IIb	No	*Cisplatin/280 mg*	X-ray, 5,000 cGy (400 cGy x 3 + 200 cGy x 19 fractions) Brachytherapy, 3,147 cGy	8.5	Hemorrhage, ulceration	2	Past use	No	No	No
PROC 095A	F	4/24/2002	Uterine corpus	Adenosarcoma	*TAH + BSO*	No	X-ray, 6,400 cGy (200 cGy x 32 fractions)	11	Pain, hemorrhage, wall changes (edematous)	1, 2	Never	No	No	Yes
PROC 096B	F	1/7/2000	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,600 cGy (200 cGy x 28 fractions) Brachytherapy, 3,100 cGy	27	Hemorrhage	2, 12 (Diet)	Never	No	No	No
PROC 097B	M	5/28/1999	Prostate	AC	No	No	X-ray, 7,400 cGy (200 cGy x 37 fractions)	61	Constipation, pain, hemorrhage, endarteritis	2, 5	Past use	No	Yes	No
PROC 098A	M	2/13/2002	Prostate	AC	No	*Neoadjuvant hormonal therapy*	X-ray, 7,200 cGy (180 cGy x 40 fractions)	10.5	Cramping, pain, hemorrhage, hypocellularity, hypovascularity, wall changes (edematous)	2, 5	Past use	No	No	No
PROC 099A	F	12/6/2000	Uterine cervix	SCC/IIb	No	*Cisplatin/ 170 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,990 cGy	16	Diarrhea, pain, hemorrhage	2	Never	No	No	No
PROC 100A	F	11/7/2002	Uterine cervix	AC	No	*Cisplatin/ 360 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,521 cGy	10.5	Hemorrhage, ulceration	2	Never	No	No	Yes
PROC 101A	F	9/3/2002	Uterine cervix	SCC/IIb	No	*Cisplatin/ 190 mg*	X-ray, 4,230 cGy (176.2cGy x 24 fractions) Brachytherapy, 4,500 cGy	20.5	Diarrhea, cramping, pain	2, 3, 5	Current use	Yes	No	No

(*Continued*)

Table 3. Patient demographics (*continued*)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments			Time to LENT diagnosis (*mo*)*	LENT presentation	Previous LENT treatment†	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
					Surgery (type)	*Chemotherapy (type/dose)*	*RT/dosage*							
PROC 102A	M	1/28/2003	Prostate	AC	No	No	X-ray, 7,000 cGy (200 cGy x 35 fractions)	18	Constipation, pain, hemorrhage, ulceration	1, 2, 3	Current use	No	No	No
PROC 103B	F	4/26/2003	Uterine cervix	SCC/IIIb	No	*Cisplatin/ 55 mg*	X-ray, 6,750 cGy (250 cGy x 27 fractions)	17	Cramping, pain, hemorrhage	2	Past use	No	No	Yes
PROC 104B	F	1/1/2000	Uterine cervix	AC	*TAH, pelvic node dissection and omental biopsy*	No	X-ray, 5,250 cGy (175 cGy x 30 fractions)	8	Diarrhea, cramping, ulceration, stricture, Endarteritis, hypocellularity, hypovascularity.	2, 5, 7	Never	No	Yes	No
PROC 105B	F	9/1/2000	Uterine cervix	SCC/Ib1	*TAH + BSO*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,000 cGy	13	Diarrhea, cramping, pain, hemorrhage, wall changes (edematous, fibrous), other (telangeictasia, regional atrophy)	1, 2	Current use	No	No	No
PROC 106A	F	12/21/2003	Endometrium	AC	*Radical hysterectomy + bilateral iliac lymph node dissection*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions)	9	Vomiting, constipation, pain, hemorrhage, ulceration, stricture, wall changes (edematous, fibrotic)	NA	Past use	No	Yes	Yes
PROC 107B	F	2/19/2003	Uterine cervix	SCC/IIa	No	No	X-ray, 5,800 cGy (200 cGy x 25 fractions + 800 cGy) Brachytherapy, 2,959 cGy	15.5	Hemorrhage	2, 12 (Diet)	Never	No	No	Yes
PROC 108A	F	2/8/2002	Uterine corpus	AC	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,660 cGy	12.5	Hemorrhage	2	Never	No	No	Yes
PROC 109A	F	6/10/2002	Uterine corpus	AC	*TAH + BSO*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,200 cGy	28.5	Vomiting, cramping, pain, Constipation, hemorrhage, ulceration, wall changes (edematous, fibrotic)	1, 2	Never	No	Yes	Yes

(*Continued*)

PROC 110A	F	2/13/2002	Uterine cervix	SCC/IIb	*Radical hysterectomy*	*Cisplatin/55 mg & Gemzar/175 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,585 cGy	21.5	Hemorrhage	2	Never	No	No	No
PROC 111B	F	2/20/2003	Uterine cervix	AC	*Radical hysterectomy*	*Carboplatin/ 350 mg*	X-ray, 7,000 cGy (200 cGy x 35 fractions)	12.5	Hemorrhage	2	Never	No	No	Yes
PROC 112B	F	8/8/2003	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,547 cGy	17.5	Hemorrhage	2	Never	No	No	No
PROC 113B	F	5/14/2003	Uterine cervix	SCC/IIIa	No	*Cisplatin/ 300 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,954 cGy	10.5	Hemorrhage	2	Never	No	Yes	No
PROC 114B	F	1/16/2003	Uterine cervix	SCC/IIIb	No	No	X-ray, 6,750 cGy (250 cGy x 27 fractions)	17	Diarrhea, pain, hemorrhage	2, 3, 5	Never	No	No	Yes
PROC 115A	F	4/14/2003	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,250 cGy (250 cGy x 21 fractions)	16	Diarrhea, pain, hemorrhage	2, 5	Never	No	No	Yes
PROC 116A	M	5/1/2002	Prostate	AC	No	*Hormonal therapy*	X-ray, 7,000 cGy (200 cGy x 35 fractions)	23.5	Hemorrhage, wall changes (edematous)	NA	Never	No	No	No
PROC 117A	M	8/1/1987	Colon	AC	*Resection with colostomy*	No	X-ray, dosage unknown	126	Diarrhea, cramping, pain, Constipation, hemorrhage	3, 5, 7, 9	Never	No	No	No
PROC 118B	M	5/1/2003	Prostate	AC	*Transurethral resection*	*Casodex/50 mg lucrin depot 3 M/ 11.25 mg*	X-ray, 6,480 cGy (180 cGy x 36 fractions)	17	Constipation, pain, Hemorrhage, ulceration, Wall changes (Pale, edematous, Fibrotic)	2	Never	Yes	No	No
PROC 119B	F	1/24/2004	Uterine cervix	SCC/Ib1	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,900 cGy	10.5	Diarrhea, hemorrhage	2	Never	No	No	No
PROC 120A	M	NA	Prostate	AC	No	No	X-ray, 6600 cGy (200 cGy x 33 fractions)	NA	Diarrhea, cramping, pain	NA	Never	No	No	No
PROC 121B	F	6/6/2003	Uterine cervix	SCC/Ib2	*TAH*	*Cisplatin/330 mg*	X-ray, 5199cGy (173.3cGy x 30 fractions) Brachytherapy, 1,800 cGy	17.5	Diarrhea, cramping, pain, constipation, ulceration, stricture, wall changes (edematous, mucosal thickening)	5, 12 (Analgesic: morphine)	Never	No	No	No

(*Continued*)

Table 3. Patient demographics (*continued*)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments			Time to LENT diagnosis (*mo*)*	LENT presentation	Previous LENT treatment†	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
					Surgery (type)	*Chemotherapy (type/dose)*	*RT/dosage*							
PROC 122A	F	1/14/2002	Uterine cervix	SCC/IIIb	No	*Carboplatin/ 1505 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,860 cGy	18	Diarrhea, hemorrhage	2	Never	No	No	No
PROC 123A	F	3/14/2002	Uterine cervix	SCC/IIb	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,750 cGy	18.5	Diarrhea, pain, hemorrhage, ulceration, wall changes (fibrotic)	1, 2, 3, 5	Never	No	Yes	Yes
PROC 124B	F	9/22/2003	Uterine cervix	SCC/IIb	No	*Carboplatin/ 600 mg*	X-ray, 5,000 cGy (400 cGy x 3 + 200 cGy x 19 fractions) Brachytherapy, 3,311 cGy	7.5	Diarrhea, hemorrhage	2	Never	No	No	No
PROC 125B	F	1/27/1987	Uterine cervix	SCC/IIIb	*Staging laparotomy, debulking of enlarged nodes in pelvis and transposition of left ovary*	No	X-ray, 5220 cGy (180 cGy x 29 fractions) Brachytherapy, 2,100 cGy	155	Diarrhea, cramping, pain, wall changes (edematous)	1, 2, 5	Current	No	No	No
PROC 126B	F	7/15/2003	Uterine cervix	SCC/IIa	*TAH + BSO*	*Cisplatin/ 120 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,000 cGy	12	Cramping, pain, hemorrhage	2, 3, 5	Never	No	Yes	Yes
PROC 127A	F	1/1/2004	Uterine cervix	SCC/IIIb	No	No	X-ray, 6,750 cGy (250 cGy x 27 fractions)	9	Pain, hemorrhage	2, 3, 5	Never	Yes	Yes	Yes
PROC 128A	F	8/1/2003	Uterine cervix	SCC/Ib2	No	*Cisplatin/ 330 mg*	X-ray, 5,600 cGy (200 cGy x 28 fractions) Brachytherapy, 3039 cGy	14	Constipation, hemorrhage	2	Never	No	No	No
PROC 129B	F	10/8/2003	Uterine cervix	ASCC/IIIb	No	*Cisplatin/ 330 mg*	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 2879 cGy	11.5	Hemorrhage	2	Never	No	No	No
PROC 130A	F	4/4/2004	Uterine cervix	SCC/IIb	No	*Cisplatin/ 240 mg*	X-ray, 5,000 cGy (400 cGy x 3 + 200 cGy x 19 fractions) Brachytherapy, 3,167 cGy	10	Pain, hemorrhage, ulceration	2	Never	No	No	Yes

(*Continued*)

PROC 131A	F	3/25/2002	Uterine cervix	SCC/IIIb	No	*Cisplatin/ 175 mg*	X-ray, 6,750 cGy (250 cGy x 27 fractions)	12.5	Cramping, pain, hemorrhage	2, 5, 10	Never	No	No	Yes
PROC 132B	F	2/7/1993	Uterine cervix	SCC/IIa	*TAH*	*No*	X-ray, 4000 cGy (160 cGy x 25 fractions) Brachytherapy dosage unknown	16.5	Diarrhea, cramping, pain, hypovascularity, wall changes (fibrotic, mucosal thickening)	2, 3, 5	Never	No	No	No
PROC 133B	F	11/19/2003	Uterine cervix	SCC/IIIb	No	No	X-ray, 5,400 cGy (200 cGy x 27 fractions)	15	Pain, hemorrhage	2	Never	No	No	Yes
PROC 134A	F	7/28/2003	Uterine cervix	SCC/IIb	No	*Carboplatin/ 900 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 2,156 cGy	19	Wall changes (edematous)	2	Never	No	No	No
PROC 135B	F	9/16/2003	Uterine cervix	SCC/IIIb	No	*Cisplatin/90 mg*	X-ray, 6,750 cGy (250 cGy x 27 fractions)	-	Pain, hemorrhage	2	Never	No	No	Yes
PROC 136A	F	3/8/2004	Uterine cervix	SCC/?	No	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,200 cGy	15.5	Wall changes (edematous) other (telangiectasia)	2	Never	No	Yes	No
PROC 137B	M	9/1/1999	Prostate	AC	No	No	X-ray, 6,300 cGy (210 cGy x 30 fractions)	4.5	Diarrhea, cramping, pain	2, 5	Never	Yes	Yes	No
PROC 138A	M	12/15/2000	Prostate	AC	No	*Hormonal therapy*	X-ray, 6800 cGy (200 cGy x 34 fractions)	49.5	Cramping, pain, hemorrhage	4, 5	Past use	No	No	No
PROC 139B	F	3/30/2004	Uterine cervix	SCC/Ib2	No	*Cisplatin/ 350 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,430 cGy	14	Hemorrhage	2	Never	No	No	Yes
PROC 140A	F	12/16/2003	Uterine cervix	AC	No	*Cisplatin/50 mg*	X-ray, 5,600 cGy (200 cGy x 28 fractions) Brachytherapy, 4,841 cGy	15.5	Hemorrhage, wall changes (edematous)	2	Never	Yes	No	No
PROC 141A	F	3/2/2004	Uterine cervix	SCC/IIb	No	*Cisplatin/70 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,598 cGy	12.5	Hemorrhage, endarteritis, wall changes (edematous)	2	Never	No	No	No
PROC 142A	F	4/29/2002	Uterine cervix	Squamous transitional papilar cell carcinoma	No	*Cisplatin/350 mg*	X-ray, 6,000 cGy (200 cGy x 30 fractions) Brachytherapy, 2,625 cGy	19	Hemorrhage	2	Never	No	No	Yes
PROC 143B	F	12/8/2003	Uterine cervix	SCC/IIIb	No	*Cisplatin/136 mg*	X-ray, 6,750 cGy (250 cGy x 27 fractions)	17.5	Pain, hemorrhage	2, 3	Never	No	Yes	Yes

(*Continued*)

Table 3. Patient demographics (*continued*)

Patient ID	Gender	Cancer diagnosis date	Tumor location	Cancer type/stage	Cancer treatments			Time to LENT diagnosis (*mo*)*	LENT presentation	Previous LENT treatment†	Tobacco use	Diabetes mellitus	Hypertension	Transfusions
					Surgery (type)	*Chemotherapy (type/dose)*	*RT/dosage*							
PROC 144B	M	10/14/2003	Prostate	AC	*TURP*	No	X-ray, 7,000 cGy (200 cGy x 35 fractions)	11.5	Diarrhea, pain, hemorrhage, Hypocellularity, hypovascularity, wall changes (pale)	1, 2	Never	No	No	No
PROC 145A	F	5/6/2004	Uterine cervix	SCC/IIb	No	*Cisplatin/300 mg + gemcetabine/ 1000 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, check dosage	8.5	Hemorrhage	2	Never	No	No	No
PROC 146A	M	10/17/2003	Prostate	AC	No	*No*	X-ray, 4,500 cGy (180 cGy x 25 fractions)	9	Diarrhea, cramping, pain, hemorrhage, wall changes (edematous)	2	Past use	No	Yes	No
PROC 147B	F	3/10/2003	Rectum	AC	*Low anterior resection*	*5-FU/15 g*	X-ray, 5,040 cGy (180 cGy x 28 fractions)	9.5	Diarrhea, constipation, pain, hemorrhage, ulceration	NA	Never	No	Yes	Yes
PROC 148B	F	3/26/2004	Uterine corpus	Mix mesodermal tumor (carcinosarcoma)	*TAH*	No	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,510 cGy	13.5	Diarrhea, hemorrhage	2	Never	No	No	No
PROC 149A	F	10/20/2003	Uterine cervix	SCC/IIb	No	*Cisplatin/300 mg*	X-ray, 5,000 cGy (200 cGy x 25 fractions) Brachytherapy, 3,562 cGy	23.5	Hemorrhage, endarteritis, wall changes (edematous)	2	Never	No	No	No
PROC 150B	M	12/19/2000	Prostate	AC	No	*Hormonal therapy*	X-ray, 6,600 cGy (200 cGy x 33 fractions)	-	Diarrhea, cramping, hemorrhage, wall changes (pale, fibrotic, mucosal thickening)	3, 11	Never	No	Yes	No

Abbreviations: RT = radiotherapy; LENT = late effects normal tissue; SCC = squamous cell carcinoma; AC = adenocarcinoma; BSO = bilateral salpingo-oophorectomy; TAH = total abdominal hysterectomy; ASCC = Adenosquamous cell carcinoma; FU = Fluorouracil; FA = Folinic acid; PVC = portal vein chemotherapy; TURP = transurethral resection of prostate.

* Rounded to nearest month.

† Previous LENT treatment: 1 = antibiotics; 2 = anti-inflammatory agent; 3 = antispasmodic agents; 4 = anticholinergic agents; 5 = antidiarrheal agents; 6 = intestinal bypass; 7 = intestinal resection; 8 = fistula repair; 9 = colostomy; 10 = ileostomy; 11 = fulguration; 12 = other.