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Assessment of Long-Term Rectal Function in Patients Who Received Pelvic Radiotherapy: A Pooled North Central Cancer Treatment Group Trial Analysis, N09C1

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Abstract

Purpose—Pelvic radiotherapy (PRT) is known to adversely affect bowel function (BF) and patient well-being. This study characterized long-term BF and evaluated quality of life (QOL) in patients receiving PRT.

Methods—Data from 252 patients were compiled from 2 North Central Cancer Treatment Group prospective studies, which included assessment of BF and QOL by the BF questionnaire (BFQ) and Uniscale QOL at baseline and 12 and 24 months after completion of radiotherapy. BFQ scores (sum of symptoms), Uniscale results, adverse-event incidence, and baseline demographic data were compared via *t* test, χ^2, Fisher exact, Wilcoxon, and correlation methodologies.

Results—The total BFQ score was higher than baseline at 12 and 24 months ($P<.001$). More patients had 5 or more symptoms at 12 months (13%) and 24 months (10%) than at baseline (2%). Symptoms occurring in greater than 20% of patients at 12 and 24 months were clustering, stool-gas confusion, and urgency. Factors associated with worse BF were female sex, rectal or gynecologic primary tumors, prior anterior resection of the rectum, and 5-fluorouracil chemotherapy. Patients experiencing grade 2 or higher acute toxicity had worse 24-month BF (*P* values, <.001-.02). Uniscale QOL was not significantly different from baseline at 12 or 24 months, despite worse BFQ scores.

Conclusions—PRT was associated with worse long-term BF. Worse BFQ score was not associated with poorer QOL. Further research to characterize the subset of patients at risk of significant decline in BF is warranted.

Keywords

adverse events; diarrhea; large intestine; quality of life; rectum; toxicity

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Conflict of Interest
The authors have no conflict of interest to declare.

Introduction

Pelvic radiotherapy is used in a diverse group of patients with various malignancies. The most common adverse effects involve the gastrointestinal tract and can be categorized as acute or long-term effects.

Acute gastrointestinal adverse effects due to irradiation of the small and large bowel occur during or shortly after pelvic radiotherapy and generally resolve within 6 weeks after treatment completion (1–5). Acute effects include diarrhea, cramping, and tenesmus. Predictors include patient characteristics, tumor factors, and radiation dose (6,7). Chemotherapy and surgery can also affect the timing, severity, and duration of these acute events (8). Studies have investigated the effectiveness of cholestyramine, olsalazine, sucralfate, glutamine, and octreotide to minimize acute toxicities (9–13). To date, no agent tested in a randomized controlled trial has been shown effective with an acceptable adverse-effect profile. Cholestyramine (vs placebo) did reduce diarrhea but caused unacceptable levels of abdominal cramping (9).

Long-term effects occur and persist for weeks to months after completion of treatment, may be permanent, and may have a considerable impact on quality of life (QOL). These can involve the small and large bowel, particularly the rectum. Small-bowel effects include pain, nausea, malabsorption, stricture, obstruction, fistulae, and abscesses (14). Large-bowel effects include bleeding, frequency, urgency, stricture, fistulae, and fecal incontinence (15). Chronic gastrointestinal toxicity may be a consequence of acute damage (16). Long-term bowel function after radiotherapy has been studied for rectal, prostate, and gynecologic cancers (8,17–23).

The development of late bowel toxicity is related to the radiation dose and irradiated bowel volume (24–27), resulting in recommendations of dose constraints (26,27). This relationship between dose-volume and toxicity may be further affected by characteristics of surgery, chemotherapy, sex, age, and baseline comorbid conditions.

The current study, approved by the Mayo Clinic Institutional Review Board, aimed to characterize the long-term bowel function of patients treated in 2 completed North Central Cancer Treatment Group (NCCTG) phase III, double-blind trials whose purposes were to assess effectiveness of glutamine (NCCTG 969256) (12) and octreotide (N00CA) (13). Neither trial demonstrated efficacy in the prevention of acute diarrhea associated with pelvic radiotherapy. The goals of the current study were to explore the relationship of long-term bowel function and symptoms with baseline characteristics, treatment, recorded adverse events, and QOL.

Methods

Patient Population and Treatment

The study population consisted of 254 patients. The glutamine trial accrued 129 patients from February 1998 through October 1999. Patients received oral glutamine or placebo twice daily during radiotherapy and for 2 weeks after completion of treatment. The octreotide trial accrued 125 patients from May 2002 through October 2005. Patients received subcutaneous injections of depot octreotide acetate or placebo at the beginning of radiotherapy and on day 29 of treatment. Eligibility and study treatment criteria have been reported previously (12,13). Patients had histologic proof of cancer in the pelvis and had a planned course of definitive or adjuvant treatment to 45 to 53.5 Gy in 1.7- to 2.1-Gy fractions to the entire pelvis. The superior field border could not lie superior to the L4-5

interspace, nor inferior to the sacroiliac joints. Physicians were allowed to boost primary tumor or tumor bed as indicated.

Data Collection and Assessment of Bowel Function

Baseline characteristic data were obtained. These included patient age, sex, race, primary disease site, history of rectal resection before radiotherapy, and adjunct treatment.

Toxicity was assessed during and after treatment using the National Cancer Institute Common Toxicity Criteria version 2.0 (28). Patient-reported incidence of problematic bowel function symptoms was assessed using the bowel function questionnaire (BFQ) (12,13,29) (Appendix). Brief descriptions of evaluated symptoms are in Table 1. Each study used the single-item Uniscale measure (30) to record overall QOL, on a linear scale (glutamine trial) or numeric scale (octreotide trial). Both versions of this measure have been validated and shown to be analogous to one another (31). Normative data have been reported (32). The BFQ and Uniscale, used successfully in other clinical trials (11–13), were completed at baseline, weekly during radiotherapy, weekly for 4 weeks after treatment, and at 12 and 24 months after completion of radiotherapy.

Statistical Analysis

The primary goal of this pooled analysis was to investigate long-term bowel function. The primary end point was the BFQ score at 24 months. Secondary goals and end points included investigation of BFQ score at 12 months, Uniscale score at 12 and 24 months, and relationships of both baseline characteristics and adverse events to QOL and long-term bowel function.

Individual symptoms in the BFQ were assigned a value of 1 if the symptom was experienced and the total BFQ score (sum of values) was calculated (range 0–9). The score of the Uniscale was the number indicated by the patient (range 0–100, where 100 was best QOL). Patients were categorized as having clinically deficient QOL if the Uniscale score was less than or equal to 50 (33). Changes from baseline were calculated for the total BFQ and Uniscale scores. The adverse-event profile per patient was characterized dichotomously according to the maximum adverse-event grade (<2 vs ≥ 2; <3 vs ≥ 3).

Two-sided hypotheses tests were conducted using type I error of $\alpha=0.05$. Scores and changes from baseline at 12 and 24 months were assessed using single-sample *t* tests. End points were compared between treatments and baseline characteristic categories. Kruskal-Wallis or Wilcoxon methodologies were applied to continuous end points and χ^2 or Fisher exact methodologies were applied to discrete end points. Spearman/Pearson correlations were used to determine relationships between BFQ and Uniscale scores.

Results

Two patients were excluded because of missing QOL data; therefore, 252 patients were included in this analysis. Baseline patient characteristics are presented in Table 2. BFQ results were available for 249 patients at baseline, 178 patients at 12 months, and 148 patients at 24 months. We compared the patients who completed BFQs at baseline, 12 months, and 24 months and observed no differences in the distribution of baseline characteristics of age, race, sex, prior rectal resection, 5-FU use, or location of primary tumor. Baseline Uniscale, total BFQ score, and frequency of each BFQ symptom were balanced between investigational and placebo arms (data for BFQ symptoms not shown).

No statistically significant differences were identified between intervention and placebo groups regarding mean BFQ score at 12 months (2.0 vs 1.6; $P=.31$) and 24 months (1.7 vs

1.6; *P*=.97), or change from baseline in mean BFQ score at 12 months (1.1 vs 0.5; *P*=.12) or 24 months (0.7 vs 0.5; *P*=.87). Comparisons of analogous Uniscale results also showed nonsignificant differences. Thus, the data were analyzed without separation by treatment group. Results indicate a decline in bowel function over time. Primary end point results showed patients had a mean BFQ score of 1.6 at 24 months (*P*<.001). This significant difference was also present at 12 months (1.8; *P*<.001). Significant mean BFQ changes from baseline also existed at both 24 and 12 months (0.59 and 0.80, respectively; *P*<.001).

Incidence of specific symptoms of long-term bowel dysfunction increased from baseline. Figure 1 shows the percentage of patients with each individual BFQ symptom. The most common symptom was urgency, occurring in almost half of patients at 12 months after treatment. Symptoms occurring in greater than 20% of patients were urgency, stool-gas confusion, clustering, and cramping. Statistically significant increases from baseline to 12 months were observed for total BFQ score (1.1 vs 1.8; *P*<.001), incontinence (2.4% vs 9.6%; *P*=.001), protective clothing (1.2% vs 9.1%; *P*<.001), stool-gas confusion (14.2% vs 22.7%; *P*=.02), urgency (29.0% vs 48.3%; *P*<.001), and cramping (11.7% vs 21.7%; *P*=.005). Statistically significant increases from baseline to 24 months were observed for total BFQ score (1.1 vs 1.6; *P*<.01), incontinence (2.4% vs 9.5%; *P*=.002), clustering (19.5% vs 28.4%; *P*=.04), and the need for protective clothing (1.2% vs 8.1%; *P*<.001). A slight decrease in total BFQ score occurred between 12 and 24 months (mean, 1.8 vs 1.6; *P*=.53). The incidence frequency of each BFQ symptom also decreased, although urgency had the only statistically significant decrease (48.3% vs 36.7%; *P*=.04).

Figure 2 illustrates the percentage of affected patients with number of symptoms, stratified by time point. Many patients had no symptoms at baseline, 12 months, and 24 months (n=121 [48.6%], n=64 [36.0%], and n=57 [38.5%], respectively). More patients had 5 or more symptoms at 12 months (13%) and 24 months (10%) than at baseline (2%). At baseline, 170 patients (67.5%) had a BFQ score of 0 or 1. At 12 months, 81 (65.9%) had fewer than 2 symptoms. At 24 months, 62 (61.4%) had fewer than 2 symptoms.

Baseline characteristics were assessed to determine predictiveness. Characteristics associated with worse long-term bowel function were female sex, prior anterior resection of the rectum, use of 5-fluorouracil chemotherapy, and a primary rectal tumor (Table 3).

The relationship between acute toxicity and long-term bowel function was explored. Patients with grade 3 or greater acute bowel toxicity had significantly worse long-term bowel function, as measured by BFQ score at 24 months, than their lower-grade counterparts. Acute bowel toxicity grade was the maximum grade of diarrhea, abdominal cramping, constipation, rectal bleeding, or tenesmus experienced by a patient. Patients with maximum acute bowel toxicity of less than grade 3 had a mean BFQ score of 1.23 at 24 months, whereas patients with acute grade 3 or greater toxicity had a mean score of 3.09 (*P*<.001). Patients who had grade 2 or higher toxicity also had significantly greater incidence of clustering, stool-gas confusion, liquid stools, and cramping at 12 months (*P*≤.01) (data not shown).

Uniscale scores had poor correlation with BFQ scores (r=−0.26 at 12 months; r=−.17 at 24 months). Changes from baseline in Uniscale score at 12 and 24 months were not significant. Patients with clinically deficient QOL scores at baseline did not have significantly worse mean BFQ scores than those with nondeficient QOL at 12 months (2.7 vs 1.7; *P*=.07) or at 24 months (2.2 vs 1.6; *P*=.22). Table 4 contains mean Uniscale scores according to symptom incidence. At 12 months, significantly lower Uniscale scores occurred for those experiencing nocturnal bowel movements, clustering, the need for protective clothing, stool-gas confusion, liquid bowel movements, and cramping. At 24 months, significantly lower

scores occurred for those experiencing clustering. Also at 24 months, significantly higher scores were reported by patients who did not experience a grade 2 or higher bowel toxicity grade (87.5 vs 80.6; P=.02).

Discussion

This trial aimed to define long-term bowel function after pelvic radiotherapy and to identify factors that might predict worse bowel function. We measured patient-reported symptoms, an established, effective modality for collecting adverse effect information (29,34). For our patients, pelvic radiotherapy resulted in worse long-term bowel function. Greater acute toxicity, female sex, location of primary tumor, history of rectal resection before radiotherapy, and treatment with 5-fluorouracil were all predictive of long-term bowel dysfunction. We noted improvement in the total BFQ score and diminished frequency of symptoms between 12 months and 24 months, although differences were not statistically significant. Lastly, we observed that while many patients had no late-term bowel toxicity, a small number of patients had multisymptom dysfunction (Figure 2). Removal of BFQ scores greater than 5 resulted in a mean change from baseline at 24 months of 0.2 (P=.17). Therefore, the increase in BFQ scores in a small number of patients accounted for most of the decline in bowel function in the population.

Most reports of poor long-term bowel function after pelvic radiotherapy describe postoperative patients with primary rectal cancer. Kollmorgen and colleagues (29) reported patients were more likely to have bowel dysfunction, as measured by frequency, clustering, nocturnal bowel movements, incontinence, protective clothing, and inability to defer stooling. Univariate analysis revealed age, sex, and length of follow-up on frequency of bowel movements and incontinence had no significant effects. Lundby et al (35) found that patients had significantly worse bowel function, manifested as frequency, incontinence, urgency, protective clothing use, loose consistency, and ability to differentiate between stool and gas. Univariate analysis for possible predictors of bowel function was not reported. Similarly, Dahlberg et al (36) reported that patients enrolled in the Swedish Rectal Cancer Trial had higher stool frequency and more commonly had emptying difficulties, incontinence, urgency, and toilet dependence.

The present study is unique in that patients had various primary cancers. Data were collected prospectively, eliminating potential recall bias and allowing standardized symptom reporting. Analyses were performed to identify patterns and possible predictors of bowel dysfunction to identify at-risk populations.

Inclusion of patients with various pelvic cancers allowed assessment of the association between the type of cancer treated and subsequent toxicity. Pelvic radiotherapy parameters were broadly defined. Because few patients are treated using protocols that specify radiotherapy parameters in detail, our results likely reflect what would be observed in clinical practice. A limitation of our study is that correlation between specific radiotherapy techniques and subsequent toxicity could not be determined. Despite this limitation, our investigation provides useful data that can be applied to patients receiving pelvic radiotherapy. Further investigation into the consequences of dose and field arrangement is warranted.

Similar to prior reports (29,35,36), bowel function in our population was worse 2 years after radiotherapy than at baseline. Importantly, long-term bowel symptoms persisted only in a small subset of the population. Symptoms appeared better at 24 months than at 12 months, implying that bowel function may continue to improve for at least 2 years after treatment.

This has implications for patient counseling, particularly for patients whose symptoms are severe enough to consider ostomy for symptom control.

Conclusion

Pelvic radiotherapy is associated with long-term bowel dysfunction. However, a substantial proportion of patients have no long-term symptoms and a small subset of patients have clinically significant, multisymptom dysfunction. Long-term bowel toxicity, as measured by the BFQ score, did not significantly affect patient-reported QOL. Several factors may predict long-term bowel dysfunction, including presence and severity of acute toxicity, female sex, location of primary tumor, history of rectal resection, and treatment with 5-fluorouracil. Identification of patients at high risk of long-term bowel dysfunction can direct future research toward decreasing acute rectal toxicity and provide clinicians with information relevant for patient counseling. Furthermore, we hope that this meta-analysis encourages similar research for other disease sites and treatment modalities, so that clinicians can better define and continue to improve the impact of treatment on our patients.

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Abbreviations

BFQ	bowel function questionnaire
NCCTG	North Central Cancer Treatment Group
QOL	quality of life

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Appendix

Appendix

Each of these statements or questions below describes symptoms or problems which sometimes occur in patients who have had radiation therapy.

Overall, would you say that you had problems with your bowel function in the past week?	Yes	No
1. In the past week, what is the greatest number of bowel movements you have had in a day? _____		
For questions 2–10, circle "yes" or "no" in response to each question.		
2. In the past week, have you had a problem causing you to get up at night to have a bowel movement?	Yes	No
3. In the past week, have you had a problem causing you to lose control of your bowel movements?	Yes	No
4. In the past week, have you had a problem causing you to have a bowel movement within 30 minutes of a prior bowel movement?	Yes	No
5. In the past week, have you had to wear protective clothing or a pad in case you lost control of a bowel movement?	Yes	No
6. In the past week, have you had a problem causing you to be unable to tell the difference between stool and gas?	Yes	No
7. In the past week, have you had a problem causing you to have stools that are liquid?	Yes	No
8. In the past week, have you found that once you feel the urge to have a bowel movement, you must do so within 15 minutes to avoid an accident?	Yes	No
9. In the past week, have you had cramping with a bowel movement? If yes, is your cramping: _____ Mild _____ Moderate _____ Severe	Yes	No
10. Do you ever have blood in your bowel movement? If yes, check the description that best describes the amount of blood in your bowel movement: _____ On toilet tissue only _____ Mixed with or coating bowel movement _____ Enough to turn water in toilet bowl red	Yes	No

Adapted from Kozelsky et al (12). Used with permission.

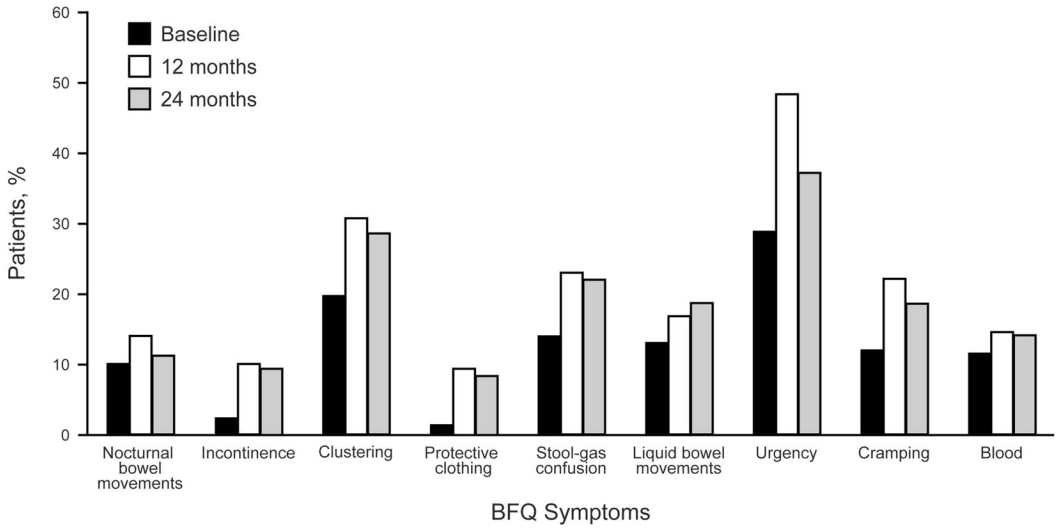

Figure 1.
Incidence of Bowel Function Symptoms. BFQ denotes bowel function questionnaire.

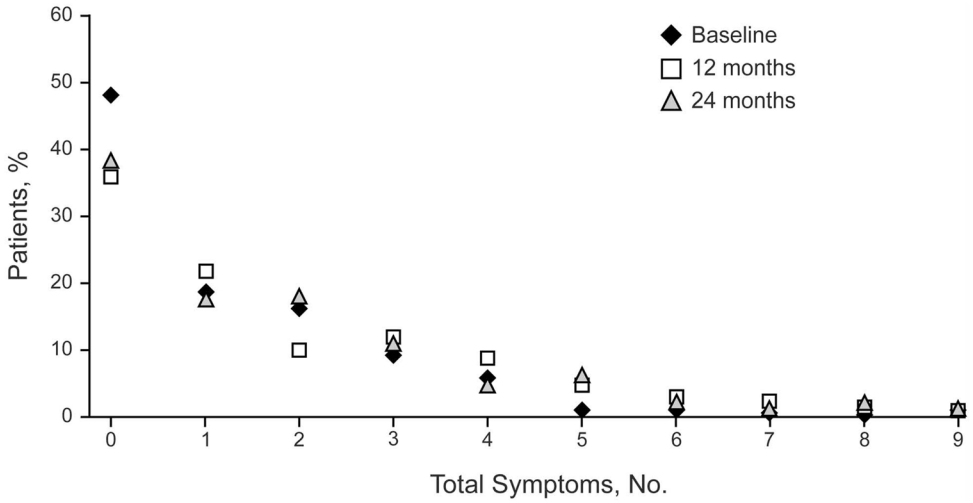

Figure 2.
Distribution of BFQ Scores. BFQ denotes bowel function questionnaire.

Table 1

Definition of Terms in the BFQ

BFQ Symptom	Definition
Nocturnal bowel movements	Needing to get up at night for bowel movements
Incontinence	Loss of control of bowel movements
Clustering	Needing to have a bowel movement within 30 minutes of a prior bowel movement
Protective clothing	Need for protective clothing or a pad
Stool-gas confusion	Unable to differentiate between stool and gas
Liquid bowel movements	Having liquid bowel movements
Urgency	Inability to delay bowel movements
Cramping	Cramping with bowel movements
Rectal bleeding	Blood with bowel movements

Abbreviation: BFQ, bowel frequency questionnaire.

Table 2

Baseline Characteristics (N=252)

Characteristic	Value
Male sex, No. (%)	161 (63.9)
Race, No. (%)	
Black	11 (4.4)
Native American	3 (1.2)
White	238 (94.4)
Age, median (range), y	66.5 (31.0–86.0)
History of rectal resection before RT, No. (%)	18 (7.1)
Treatment with 5-fluorouracil, No. (%)[c]	
None	195 (77.4)
Bolus	9 (3.6)
Continuous infusion	48 (19.0)
Primary cancer location, No. (%)	
Rectum	53 (21.0)
Prostate	122 (48.4)
Gynecologic organ	69 (27.4)
Other	8 (3.2)
Baseline BFQ score, mean[a]	1.1
Baseline QOL score, mean[b]	83.1

Abbreviations: BFQ, bowel function questionnaire; QOL, quality of life; RT, radiotherapy.

[a]Potential scores ranged from 0–9.

[b]Potential scores ranged from 0–100.

[c]Of the 57 patients treated with 5-fluorouracil, 53 had rectal cancer, 2 had anal cancer, 1 had bladder cancer, and 1 had gynecologic cancer.

Table 3

Characteristics Predictive of 24-Month Bowel Function (N=148)

Characteristic	Value		*P* Value
	Patient Sex		
	Female (n=56)	Male (n=92)	
Total BFQ score, mean	2.1	1.4	.04
Protective clothing, %	14.3	4.3	.03
Urgency, %	49.1	29.3	.02
Cramping, %	30.9	10.9	.002
	Anterior Resection of the Rectum Before RT		
	Yes (n=13)	**No (n=135)**	
Total BFQ score, mean	3.2	1.5	<.001
Nocturnal bowel movements, %	38.5	8.2	<.001
Incontinence, %	30.8	7.4	.01
Clustering, %	84.6	23.0	<.001
Liquid bowel movements, %	38.5	16.3	.048
	Chemotherapy With 5-Fluorouracil		
	Yes (n=29)	**No (n=119)**	
Total BFQ score, mean	2.5	1.4	.003
Nocturnal bowel movements, %	31.0	5.9	<.001
Incontinence, %	20.7	6.7	.02
Clustering, %	69.0	18.5	<.001
Stool-gas confusion, %	37.9	17.6	.02

Characteristic	Value				
	Location of Primary Cancer[a]			**3-Group *P* Value[b]**	**Rectum vs Prostate *P* Value[c]**
	Rectum (n=27)	**Gynecologic Organ (n=47)**	**Prostate (n=72)**		
Total BFQ score, mean	2.5	2.0	1.0	<.001	<.001
Nocturnal bowel movements, %	33.3	8.5	4.2	<.001	<.001
Incontinence, %	18.5	10.6	4.2	.03	.02
Clustering, %	70.4	27.7	11.1	<.001	<.001
Protective clothing, %	7.4	14.9	2.8	.02	.30
Stool-gas confusion, %	37.0	21.3	13.9	.004	.01
Urgency, %	46.2	46.8	25.0	.01	.04
Cramping, %	11.1	37.0	9.7	.001	.24

Abbreviation: BFQ, bowel function questionnaire; RT, radiotherapy.

[a] Two patients had a location of “other” and were excluded from this analysis.

[b] Significant *P* values indicate a difference in the incidence distributions among the 3 groups. It does not indicate pairwise differences.

[c] *P* value indicates significance of rectum vs prostate scores and frequencies.

Table 4

Effect of BFQ Symptoms on QOL Scores

	QOL Score, mean[b]					
	12 Months BFQ Symptom			24 Months BFQ Symptom		
BFQ Symptom[a]	Present	Absent	*P* Value	Present	Absent	*P* Value
Nocturnal bowel movements	75.5	84.6	.02	76.9	84.1	.06
Incontinence	79.9	93.9	.16	87.5	82.8	.46
Clustering	80.3	84.9	.03	79.7	84.8	.02
Protective clothing	69.4	85.0	<.01	86.1	83.0	.65
Stool-gas confusion	75.6	85.9	<.01	80.7	84.0	.34
Liquid bowel movements	75.5	85.0	<.01	76.8	84.8	.10
Urgency	83.1	84.3	.47	81.9	84.3	.15
Cramping	80.1	84.6	.04	81.2	84.0	.53
Rectal bleeding	75.8	84.9	.09	83.1	84.1	.42

Abbreviations: BFQ, bowel function questionnaire; QOL, quality of life.

[a] Complete description of symptoms is shown in Table 1.

[b] Possible scores ranged from 0–100 (higher values indicate better QOL).