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ORIGINAL ARTICLE

The Impact of Prebiotic, Fiber and Glutamine Supplementation on Bowel Symptoms and Quality of Life in Prostate Cancer Patients Undergoing Pelvic Radiotherapy

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OBJECTIVE

To investigate the impact of nutritional intervention based on prebiotic, fiber and glutamine supplementation on bowel symptoms and quality of life (QoL) in prostate cancer patient undergoing pelvic radiotherapy (RT).

METHODS

A total of 20 prostate cancer patients undergoing pelvic RT were included. Data on nutritional status assessment scores (SGA and NRS-2002) and QoL questionnaire (EORTC QLQ-CR29) scale were recorded prior to pelvic RT, while the bowel symptom questionnaire was repeated every week throughout the pelvic RT.

RESULTS

Increase in daily defecation frequency (85.0%) and abdominal distension (65.0%) were the most prevalent and progressed symptoms, while fecal incontinence (20.0%), anal skin wound (15.0%) and blood in stool (10.0%) were the less prevalent symptoms. Grade 3 symptoms were observed in 13(65.0%) patients including increase in daily defecation frequency in 11(55.0%) patients. No significant difference from baseline to radiotherapy weeks or between radiotherapy weeks was noted in QoL scores.

CONCLUSION

Our findings revealed that the concomitant FOS, GOS, fiber and glutamine based nutritional intervention can be an efficient intervention for reduction of certain bowel symptoms and the maintenance of QoL scores throughout the pelvic RT in prostate cancer patients.

Keywords: Fiber; glutamine; nutritional intervention; pelvic radiotherapy; prebiotic; prostate cancer.

INTRODUCTION

Prostate cancer is the most common malignancy among males.[1] Although the early detection and advances in treatment have enabled an improved survival in prostate cancer patients,[2] the urinary, sexual, and bowel dysfunction symptoms related to disease itself or treatment side effects remain to be significant determinants of patient's health-related quality of life (HRQOL).[3]

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Pelvic radiotherapy (RT), a well-established treatment option with technically advanced delivery in patients with intermediate or high-risk prostate cancer, may cause acute and late onset bowel symptoms (i.e., diarrhea, abdominal pain, and urgency) related to radiation-induced enteritis as associated with significant morbidity and mortality as well as the adverse impacts on QoL.[4,5]

Besides the detrimental effects of radiotherapy-induced damage to gastrointestinal mucosa on nutrient absorption and digestion,[6] data from the studies in the oncology setting also revealed the prevalence of malnutrition to range from 11 to 30% in patients receiving radiotherapy.[7] Therefore, given that bowel symptoms and malnutrition appear together in the oncological patient due to disease itself or the administered treatments, provision of nutritional intervention to limit the acute inflammatory processes during radical pelvic RT is considered an attractive option for the prevention of the bowel symptoms as well as the concomitant malnutrition risk.[6]

Although nutrition interventions such as elemental diet, fiber supplementation, lactose restriction and modification of fat and fiber intake have been investigated in terms of their effect in reducing the bowel symptoms from pelvic RT,[5,8,9] there is insufficient high-grade evidence to routinely recommend nutritional intervention during pelvic RT.[6]

Owing to current evidence on the link between the pathobiology of radiation-induced gastrointestinal symptoms and gut microbial dysbiosis, the potential utility of food supplements such as probiotics, prebiotics, and vitamins as promising actors for prevention and/or treatment of bowel symptoms have become increasingly studied in patients undergoing pelvic RT.[10] Prebiotics, by providing a substrate for the preferential growth of nonpathogenic species resulting in the enhanced production of short chain fatty acids (SCFA), promote optimal colonic fluid balance, stimulate water and sodium absorption and preserve mucosal barrier function.[6,11] Fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) are prebiotics that allow specific changes in the composition and/or activity in the gastrointestinal microbiota that positively contribute to host well-being and health.[6,12]

Although a beneficial effect of provision of a modified fiber or lactose intake on bowel symptoms has been suggested in prostate cancer patients undergoing pelvic RT, there is limited number of investigations along with no data on the potential effect of nutritional intervention with GOS or FOS supplementation.[5,13] Accordingly, there is lack of consensus on the appropriate nutritional intervention with benefits in reducing bowel symptoms from pelvic RT, specifically in prostate cancer patients.[5,6]

This study was designed to investigate the impact of nutritional intervention based on prebiotics (GOS, FOS), fiber and glutamine supplementation on bowel symptoms and QoL in prostate cancer patient undergoing pelvic RT.

MATERIALS AND METHODS

Study Population

A total of 20 consecutive prostate cancer patients undergoing pelvic regional RT were included in this prospective cross-sectional study conducted at a tertiary care radiation oncology clinic.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki".

Assessments

Data on patient age, the nutritional status screening scores including Subjective Global Assessment (SGA) and Nutritional Risk Screening 2002 (NRS-2002), European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Colorectal Cancer (EORTC QLQ-CR29) scale were recorded prior to pelvic RT. The bowel symptom questionnaire that elicited bowel-specific items of EORTC QLQ-CR29 was repeated every week throughout the prostate radiotherapy. Change in bowel symptoms from baseline was evaluated at each week of pelvic RT.

Bowel Symptom Questionnaire

Bowel symptom questionnaire included the 10 items of the EORTC QLQ-CR29 questionnaire, which specifically addresses the bowel symptoms (anal pain, bloating, blood in stool, mucus in stool, gas incontinence, fecal incontinence, anal skin wound, daytime defecation, nighttime defecation and increase in bowel movements).[14] Accordingly, pre-treatment and weekly treatment prevalence of bowel symptoms were recorded, and each item was scored via 1 (none) to 4 (frequent) Likert scale with higher scores indicating a higher level of gastrointestinal discomfort. The reliability and validity analysis of Turkish version of The EORTC QLQ-C29 was performed.[15] In addition, physicians assessed toxicity using Common Terminology Criteria for Adverse Events (CTCAE) v.5.0.

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Table 1 The prescribed doses for target volumes and the dose-volume parameters of intestinal critical organs

Volume parameters	Mean (±SD) (min-max)
The dose of elective regional volume (median)	50 Gy (50–54 Gy)
The dose of prostate volume (median)	
Prostate bed (n=12)	70 Gy (66–70 Gy)
Prostate (n=8)	74 Gy (72–74 Gy)
Bowel V_{45Gy} (cc)	67.46 (±40.35) (22–142)
Bowel D_{max} (Gy)	54.76 (±3.34) (48–58.85)
Rectum V_{40Gy} (%)	39.74 (±9.52) (21.44–60.81)
Rectum V_{50Gy} (%)	20.76 (±7.11) (5.46–34.66)
Rectum V_{60Gy} (%)	7.33 (±4.32) (1.19–17.56)
Rectum V_{65Gy} (%)	2.97 (±2.86) (0.04–10.22)
Rectum V_{70Gy} (%)	0.75 (±1.19) (0–4.48)
Rectum D_{max} (Gy)	72.64 (±3.54) (67.10–80.61)
Rectum D_{mean} (Gy)	36.25 (±3.87) (28.64–43.38)

SD: Standart deviation; VxGy: Fraction of volume that received a dose of ≥X Gy; D_{max}: Maximum dose of volume; D_{mean}: Mean dose of volume

Nutritional Status Assessment and Nutritional Support

Pre-radiotherapy nutritional status assessment was based on SGA and NRS-2002 tools. Patients with NRS 2002 scores ≥3 were considered to be at risk of malnutrition necessitating the provision of nutritional intervention. Based on SGA scores, patients were classified as SGA-A (well-nourished), SGA-B (mildly/moderately malnourished), SGA-C (severely malnourished).

All patients received additional nutritional support with once-a-day Fortimel Compact Fiber (2.4 kcal/mL, Nurticia®) containing FOS, GOS and fiber and three times a day Glutamine Plus (22.4 g sachets, Fresenius Kabi®) during the radiotherapy period, independent from nutritional status.

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Descriptive statistics are reported including percentages for categorical variables. Chi-square (X^2) test was used for the comparison of categorical data, while parametric variables were analyzed using MANOVA test. $p<0.05$ was considered statistically significant.

RESULTS

All patients received pelvic irradiation to the regional elective nodes. The median pelvic dose was 50 Gy. Twelve patients received salvage or adjuvant radiotherapy after radical prostatectomy. Dose-volume histogram parameters of intestinal organs summarized in Table 1.

Table 2 Patient characteristics and nutritional status

Patient characteristics (n=17)	Mean (SD) (min-max)	
Age (year)	67.5 (7.9) (50.0–81.0)	
Height (cm)	172.4 (6.9)	
Weight (kg)	82.8 (11.1)	
BMI (kg/m²)	27.8 (3.3)	
	n	**%**
Nutritional assessment (n=17)		
NRS-2002 score	1.4 (0.5) (1.0–2.0)	
NRS <3	17	100.0
NRS ≥3, (malnutrition risk)	0	0.0
SGA category		
SGA-A (well-nourished)	17	100.0
SGA-B (mildly/moderately malnourished)	0	0.0
SGA-C (severely malnourished)	0	0.0

SD: Standard deviation; BMI: Body mass index; NRS: Nutritional Risk Screening; SGA: Subjective Global Assessment

Mean patient age was 67.5 (7.9 range, 50 to 80) years and Body Mass Index (BMI) was 27.8 (3.3) kg/m². At baseline, none of the patients were malnourished (all patients were in SGA-A category) or at risk of malnutrition (NRS scores were <3 in all patients) (Table 2).

Mean (SD) total QoL and bowel symptom scores were 31.6 (6.1) and 13.1 (2.8) overall, with no significant difference from baseline to radiotherapy weeks or between radiotherapy weeks in terms of QoL and bowel symptom scores (Table 3).

Table 3 Total QoL and bowel symptom scores during the study period

	Total QoL scores		Bowel symptom scores	
	N	Mean (SD)	N	Mean (SD)
Baseline	20	28.6 (4.7)	20	10.8 (0.9)
During RT				
Week 1	20	29.2 (4.6)	20	12.2 (1.9)
Week 2	19	30.6 (5.5)	19	12.9 (2.4)
Week 3	20	32.8 (6.1)	20	13.6 (2.9)
Week 4	18	32.8 (6.8)	18	13.8 (3.2)
Week 5	14	33.1 (6.7)	14	14.6 (3.2)
Week 6	12	33.7 (7.4)	12	14.5 (3.4)
Week 7	7	36.4 (4.7)	7	14.9 (1.9)
Total		31.6 (6.1)		13.1 (2.8)
p value		0.374		0.239

MANOVA test. QoL: Quality of life; SD: Standard deviation; RT: Radiotherapy

The prevalence of bowel symptoms significantly increased from baseline with the onset of radiotherapy (from 55.0% to 100.0%, p<0.001). All patients reported emergence of a new symptom or worsening of existing symptoms under pelvic RT with a median progression score of 3.5 (range, 1.0 to 11.0) (Table 3).

In 9 (45.0%) of 20 irradiated prostate cancer patients, bowel symptoms progressed most prominently at week 3 or week 4 of radiotherapy. Increase in daily defecation frequency (85.0%) was the mostly progressed symptom, as followed by abdominal distension (65.0%), anal pain (55.0%), gas incontinence (55.0%) and increased bowel movements (50.0%). Fecal incontinence (20.0%), anal skin wound (15.0%) and blood in stool (10.0%) were the least prevalent symptoms throughout the pelvic RT (Table 3).

Score 3 (complaint at a level of quite a bit according to EORTC QLQ-CR29 questionnaire) symptoms were observed in 13 (65.0%) patients including increase in daily defecation frequency in 11 (55.0%) patients (Table 4).

DISCUSSION

Our findings in prostate cancer patients undergoing pelvic RT revealed that none of patients were malnourished or at risk of malnutrition at the onset of radiotherapy, and nutritional intervention via GOS-FOS-fiber-glutamine supplementation during pelvic RT was associated with maintenance of QoL scores and a lower rate of certain bowel symptoms (i.e. fecal incontinence, anal skin wound and blood in stool rather than diarrhea, abdominal distension, anal pain, gas incontinence and increased bowel movements).

In a 1-day analysis of the prevalence of malnutrition study in different types of cancer patients (n=1903), authors reported that overall, 39% of patients were malnourished, while prostate cancer was associated with the lowest prevalence of malnutrition (13.9%) as compared with other cancer types.[16] None of prostate cancer patients were malnourished or at risk of malnutrition at the time of radiotherapy planning in the current study.

In the current study, bowel symptoms such as increase in daily defecation frequency (diarrhea) and abdominal distension were the most prevalent symptoms, particularly during the first 4 weeks of radiotherapy, while fecal incontinence, anal skin wound and blood in stool were the least prevalent symptoms. Hence, concomitant nutritional support with once-a-day Fortimel Compact Fiber (FOS, GOS and fiber) plus glutamine during the period of pelvic RT seems to be associated with relatively lower likelihood of fecal incontinence, anal skin wound and blood in stool. Similarly, in a past study on the effects of a nutrition intervention (NI group, n=92, soluble fibers and reduced intake of lactose) vs. standard care (SC group; n=88) on bowel symptoms and HRQOL, up to 24 months after radiotherapy completion in prostate cancer patients, diarrhea was reported to be the most prevalent symptom during the acute phase (76% in the NI and 69% in the SC group), while blood in stools was less prevalent in the NI group.[5] The authors also noted that most symptoms worsened during the acute phase (up to 2 months post radiotherapy) and improved during the late phase (7 to 24 months post radiotherapy) in both the intervention and standard care groups.[5] Hence, the authors concluded that their results on nutrition intervention via transition to foods with higher proportion of soluble fiber and low in lactose do not support routine nutrition intervention of this type to reduce adverse effects from pelvic RT, as it was associated with continuation of diarrhea as the most prevalent bowel symptom but less blood in stools and more bloated abdomen.[5]

Also, in a past study on the long-term effects of dietary intervention (n=64, reduced insoluble dietary fiber and lactose intake) vs. standard care group (n=66, usual diet) on gastrointestinal symptoms and HRQOL after highly dose-escalated RT in prostate cancer patients, dietary intervention had no obvious effect on long-term gastrointestinal symptoms or HRQOL.[13] The authors also noted that the vast majority of long-

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Table 4 Bowel symptom frequency and progression during radiotherapy

	Baseline		Under radiotherapy	
	n	%	n	%
Bowel symptoms				
No	9	45.0	0	0.0
Yes	11	55.0	20	100.0
p value (χ^2 test)	**<0.001**			
Emergence of a new symptom or progression of existing symptoms under radiotherapy				
Yes	20	100.0		
Progression score				
Mean (SD)	4.3 (2.9)			
Median (min-max)	3.5 (1.0–11.0)			
Week of the most prominent progression				
Week 1	1	5.0		
Week 2	4	20.0		
Week 3	5	25.0		
Week 4	3	15.0		
Week 5	3	15.0		
Week 6	2	10.0		
Week 7	2	10.0		
Progressed symptoms				
Item 20 (increase in daily defecation frequency)	17	85.0		
Item 6 (abdominal distension)	13	65.0		
Item 5 (anal pain)	11	55.0		
Item 17 (gas incontinence)	11	55.0		
Item 22 (increased intestinal motility)	10	50.0		
Item 18 (fecal incontinence)	4	20.0		
Item 19 (anal skin wound)	3	15.0		
Item 7 (blood in stool)	2	10.0		
Score 3 bowel symptoms	13	65.0		
Item 20 (daily defecation frequency)	11	55.0		
Item 6 (bloating)	4	20.0		
Item 5 (anal pain)	3	15.0		
Item 8 (mucus in stool)	3	15.0		
Item 17 (gas incontinence)	2	10.0		
Item 22 (increased bowel movements)	3	15.0		

SD: Standard deviation

term gastrointestinal symptoms were reported as "a little", with a noticeable difference from baseline only for fecal incontinence, limitations on daily activities, and mucus discharge. The authors concluded that long-term gastrointestinal symptoms were predominantly mild, and dietary intervention was not superior to a usual diet in preventing these symptoms.

In two case series, favorable effects of both reduced[17] and increased[18] fiber consumption during pelvic RT were reported in prostate cancer patients. In a large retrospective study imposed dietary restrictions (low residue, restricted caffeine, alcohol and spicy foods) in 156 prostate cancer patients, authors reported improved genitourinary and gastrointestinal symptoms in compliant vs. noncompliant patients, while all noncompliant patients experienced side effects and grade 1 toxicity (41% of patients) easily managed by reinforcement of dietary advice.[17] In the smaller prospective study in 22 prostate cancer patients, individual advice to increase dietary fiber and fluid with the aim of stabilizing rectal dimensions to prevent prostate deformation during treatment was reported to be associ-

ated with improved HRQOL measured via inflammatory bowel disease questionnaire (IBDQ-B).[18]

In the current study, increase in daily defecation frequency (diarrhea) was responsible for the majority of overall and grade 3 symptoms. In fact, grade 1–2 diarrhea was more frequent in our study compared to the literature (p=0.004, with binomial analysis), which may be explained by use of a larger irradiated volume or a lower patient tolerance in our study. It should also be noted that at least half of patients in our study had pre-existing bowel symptoms, which has been associated with an increased likelihood of bowel symptoms during both the acute and the late phases of RT.[5,19] Given that severe acute symptoms also increase the risk of late bowel symptoms (i.e., diarrhea, urgency, rectal bleeding and incontinence) that persist or develop months to years after RT and affect the QoL in a considerable portion of patients,[20] our findings may indicate the potential benefit of screening for pre-existing bowel symptoms before RT and targeting tailored nutritional intervention to patients with symptoms.[5]

Given the maintenance of QoL throughout the radiotherapy despite emergence of new bowel symptoms or progression of pre-existing bowel symptoms in all of our patients, our findings support the consideration of HRQOL to be generally high among irradiated prostate cancer patients despite the consideration of symptoms such as bowel and urinary problems and sleep disturbances to be more pronounced.[21,22] In fact, amongst anorectal symptoms after irradiation of the prostate, rectal blood loss and fecal incontinence have been considered as the ones with a more serious impact on quality of life (QoL). Thus, maintenance of QoL scores during the radiotherapy in our prostate cancer patients may also be associated with the fact that fecal incontinence and blood in stool were the least prevalent symptoms in our patients who received additional nutritional support during pelvic RT.

Indeed, according the CTCAE version 5.0 scale assessment by physicians, none of the patients had grade 3 and above complication in our study. Similarly, in a study with 394 prostate cancer primarily treated with high-dose, image-guided radiotherapy (IGRT)/intensity-modulated radiotherapy (IMRT), no grade 3 gastrointestinal acute and late toxicity were detected, and authors considered that high dose RT was a safe and efficient treatment with low toxicity profile.[23] Indeed, a discordance between physician-based assessments and patient reported outcomes (PRO) in assessing bowel symptoms after RT for prostate cancer has also been emphasized.[19] In a past study with 75 prostate cancer patients who received RT, based on Late Effects in Normal Tissues-Subjective, Objective, Management and Analytic scales (LENT-SOMA) and Expanded Prostate Cancer Index Composite (EPIC) questionnaires and physician-based assessment of toxicity using CTCAE v.4.0., authors noted that correlation between physician and PRO was poor for most symptoms and the physician-based assessment of toxicity using CTCAE revealed that acute toxicity during radiotherapy was very low. [19] The authors also noted that the significant increase in fecal urgency after radiotherapy was only detected by the additional questions and not by the physicians or PRO questionnaires, emphasizing the use of improved tools in assessing bowel toxicity to identify those patients who may have symptoms with an impact on their QoL.

During fractionated pelvic RT, delivered daily over treatment periods of 5–7 weeks, up to 90% of patients are considered to experience symptoms, mainly the change in bowel habit (94%), loose stool (80%), bowel frequency (74%), urgency (39%) and fecal incontinence (37%).[24] Accordingly, our findings indicate the utility of a nutritional intervention based on provision of GOS, FOS, fiber and glutamine containing nutritional products in prostate cancer patients undergoing pelvic RT in terms of maintenance of overall QoL, possibly linked to amelioration of the bowel symptoms with stronger impact of QoL (i.e., fecal incontinence and blood in stool) relative to other bowel symptoms (i.e., diarrhea and abdominal distension).

Indeed, in a systematic review of studies on the efficacy of nutritional interventions to counteract acute gastrointestinal toxicity during therapeutic pelvic RT, authors concluded that there is insufficient high-grade evidence to recommend nutritional intervention during pelvic radiotherapy, with potential role of only total replacement of diet with elemental formula or use of probiotics.[6]

Certain limitations to this study should be considered. First, due to the cross-sectional design it is impossible to establish any cause-and-effect relationships. Second, potential lack of generalizability seems another important limitation due to single center study design with relatively small sample size. Third, nutritional screening was based on single-point assessment with no data on follow up status with respect to provision of nutritional support. Fourth, lack of control group of patients who received pelvic RT alone without a nutritional intervention is another limitation which otherwise would extend the knowledge achieved in the current study.

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CONCLUSION

In conclusion, our findings revealed increase in daily defecation frequency and abdominal distension remained to be the most prevalent and worsening bowel symptoms in irradiated prostate cancer patients, despite the provision of additional nutritional support with prebiotic, fiber and glutamine supplementation during period of pelvic RT. Nonetheless, fecal incontinence, anal skin wound and blood in stool were the least prevalent symptoms along with the maintenance of QoL scores throughout the pelvic RT, indicating potential benefit of concomitant FOS, GOS, fiber and glutamine based nutritional intervention in reduction of certain bowel symptoms during pelvic RT in prostate cancer patients. There is a need for larger scale randomized trials addressing the impact of different nutritional interventions on acute and late onset bowel symptoms related to extended field RT for prostate cancer.

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