Randomized controlled trial of dietary fiber for the prevention of radiation-induced gastrointestinal toxicity during pelvic radiotherapy

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Abbreviations:

ANOVA	Analysis of Variance
AOAC	Association of Official Analytical Chemists
AUC	Area under the Curve
BMI	Body Mass Index
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
EBRT	External Beam Radiotherapy
g/d	grams/day
Gy	Gray
$HgCL_2$	Mercuric Chloride
HMG CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
H_2PO_4	Dihydrogen Phosphate
IBDQ	Inflammatory Bowel Disease Questionnaire
IBDQ-B	Inflammatory Bowel Disease Questionnaire – Bowel
IMRT	Intensity Modulated Radiotherapy
ITT	Intention to Treat
IV	Intravenous
NHS	National Health Service
NSP	Non-starch polysaccharide
RCT	Randomized Controlled Trial
RT	Radiotherapy
SCFA	Short Chain Fatty Acids
SD	Standard Deviation

Abstract

Background

Therapeutic radiotherapy is an important treatment for pelvic cancers. Historically, low fiber diets have been recommended to prevent gastrointestinal toxicity despite a lack of evidence and potential mechanisms through which fiber might be beneficial.

Objective

This two-center, 3-arm, randomized controlled trial compared high, low and habitual fiber diets for the prevention of gastrointestinal toxicity in patients undergoing pelvic radiotherapy (RT).

Design

Patients were randomized to high fiber (target ≥18 g/d non-starch polysaccharide, NSP), low fiber (≤10 g/d NSP) or habitual fiber (control) diets and received individualized dietician-led counseling at the start of radiotherapy to achieve these targets. Gastrointestinal toxicity was measured using the Inflammatory Bowel Disease Questionnaire – Bowel (IBDQ-B) score. Daily fiber intake, stool diaries and SCFA were analyzed at start and end of radiotherapy.

Results

A total of 166 patients were randomized (high fiber 56, low fiber 55, control 55). Fiber intakes were significantly different between groups ($p<0.001$). IBDQ-B scores reduced (worsening symptoms) in all groups during radiotherapy but the reduction was smaller in the high fiber group (mean -3.7, SD ± 13.0) compared with control (-10.8, SD ± 13.6, $p=0.011$). Significant within group reductions occurred in total energy and protein intake in the low fiber group ($p=0.019$ and $p=0.002$) and control groups ($p=0.010$; $p=0.006$). No significant differences were observed in stool frequency, form or SCFA concentrations. At 1-year post-RT (n=126) the difference in IBDQ-B scores between the high fiber (+0.1 ± 14.5) and control (-8.4 ± 13.3) groups was significant ($p=0.004$). No

differences in IBDQ-B scores were identified between the low fiber and control groups.

Conclusions

Dietary advice to follow a high fiber diet during pelvic radiotherapy resulted in reduced gastrointestinal toxicity both acutely and at one year compared with habitual fiber intake. Restrictive, non-evidence based advice to reduce fiber intake in this setting should be abandoned.

Key words: gastrointestinal, toxicity, radiotherapy, pelvic, cancer, pelvic radiation disease, fiber, fibre, non-starch polysaccharide, NSP, short chain fatty acids, SCFA, Inflammatory Bowel Disease Questionnaire, IBDQ, IBDQ-B

Introduction

Radiation therapy is used in at least 50% of cancer patients and plays a critical role in 25% of cancer cures. It is estimated that in the US, approximately 300,000 patients per annum receive radiotherapy for pelvic or abdominal malignancies (1, 2). In the UK, there are in excess of 110,000 new pelvic cancer diagnoses a year, with an estimated 17,000 patients receiving radical (curative) radiotherapy (3). Despite major advances in the planning, verification and delivery of radiotherapy, radiation-induced gastrointestinal toxicity is common. Acutely (during treatment), 90% of patients experience changes in bowel habit including loose stool, frequency, flatulence, urgency and incontinence (4). Delayed intestinal radiation toxicity is a progressive condition with few therapeutic options and substantial long-term morbidity and mortality (5). Currently there are an estimated 1.6 million Americans living with post-radiation intestinal dysfunction (1). It is not known to what degree modern innovation in radiation technique will reduce the severity of acute and chronic toxicity but it is unlikely ever to abolish it completely.

There are only a small number of therapeutic strategies for radiation-induced gastrointestinal toxicity, and those that are available have limitations. The free radical scavenger, amifostine is the only FDA-approved agent for use in this setting but concerns remain regarding its side-effects and its potentially tumour-protective properties (1). Dietary strategies have been trialed primarily as prophylactic agents but with limited success (6), although lack of evidence for their efficacy may be partly explained by the poor quality of many studies and the acknowledged difficulties of undertaking robust, placebo-controlled dietary interventions (7). Clinical benefit for the manipulation of dietary fiber is inconclusive. Four randomized controlled trials have

been conducted recruiting 264 patients in total (8-11). Three used pharmaceutical fiber supplements in combination with low fat or low lactose diets (8, 9, 11) whilst another used a low fiber diet in combination with a low lactose diet (10) thus limiting the conclusions that could be drawn. Despite a lack of evidence, anecdotal evidence suggests many patients are encouraged to reduce their fiber intake during pelvic radiotherapy.

It can be hypothesized that high fiber intake during pelvic radiotherapy may be potentially beneficial via multiple mechanisms. Fermentable (soluble) fiber provides a substrate for the production of short-chain fatty acids (SCFA) which have multiple beneficial effects on gut health (12) promoting sodium and associated water uptake and having specific anti-inflammatory activity (13). Butyrate in particular is a primary substrate for colonocyte metabolism and therefore involved in the maintenance of colonic integrity (12), including preservation of tight junctions and prevention of para-cellular permeability. The gastrointestinal mucosal response to radiation is pro-inflammatory (14) and has many pathological parallels to inflammatory bowel disease (15), where high fiber interventions have been shown to be effective in the treatment and maintenance of ulcerative colitis and pouchitis (16).

The primary aim of this randomized controlled trial was to test the hypothesis that a high fiber diet would prevent or reduce acute and chronic radiation-induced gastrointestinal toxicity in patients undergoing radiotherapy for pelvic cancers. Its secondary objectives were to examine clinical outcomes of importance to patients including quality of life, effect of dietary fiber manipulation on stool frequency and form (consistency) and impact on nutritional outcomes.

Subjects and Methods

This two-center, three-arm (high fiber, low fiber, habitual fiber), randomized controlled trial (US NIH Trial ID: NCT 01170299) was conducted in compliance with CONSORT recommendations (17). It was approved by the institutional committees for clinical research and ethical consent was granted by the local Research Ethics Committee.

Patients and radiotherapy protocols

Patients were recruited from the Royal Marsden NHS Foundation Trust, Sutton, Surrey and London and from the Royal Surrey County Hospital, Guildford, Surrey. Eligible patients were those with histologically proven gynecological or lower gastrointestinal cancer, due to receive radical (curative) radiotherapy to the pelvis, with or without concomitant chemotherapy and able to tolerate 100% oral diet. Those with established wheat intolerance or celiac disease, a gastrointestinal stent, a gastrointestinal stoma or enrolled in other trials with conflicting toxicity end-points were excluded.

Radiotherapy treatment (all pelvic sites) was delivered using using External Beam (EBRT) or Intensity Modulated (IMRT) radiotherapy techniques (**Table S1**). All patients received at least 45 Gray (Gy) to the pelvis in 1.8 Gy daily fractions, 5 times per week, over 5 to 7 weeks. Patients with gynecological cancers received high or low dose adjuvant brachytherapy where indicated. Concomitant chemotherapy comprised oral daily capcitabine, mitomycin C in combination with oral capcitabine and weekly IV cisplatin for colorectal, anal and cervical cancers respectively.

Trial design

Informed signed consent was obtained prior to any study related procedures. Following collection of baseline data, patients were allocated to study group using the

minimization method, by the Institute of Cancer Research Randomization Unit, stratified by pelvic site and receipt of concomitant chemotherapy. The three study groups comprised: [1] habitual or *ad-libitum* diet (control group); [2] low fiber diet (non-starch polysaccharide, NSP, target ≤10 g/d); [3] high fiber diet (NSP, target ≥18 g/d). Patients and investigators were unblinded to intervention.

Patients in all study groups received an enrollment (start of treatment) and exit (end of treatment) interview with the study dietician and a minimum of two on-treatment interviews, each of 20 – 30 minutes duration during their radiotherapy. Interviews were designed to allow for collection of study outcome measurements and to review compliance with treatment allocation (i.e. fiber targets). At the enrollment interview, patients allocated to the high or low fiber groups were given a daily fiber target and counseled on how to achieve this target. Counseling comprised an individualized discussion regarding usual food choices, with emphasis on fiber-rich foods and an agreement as to how to adjust these choices to achieve their prescribed target. In addition, they were given educational / recording items including a bespoke 'Fiber in Foods' booklet detailing the fiber content in 'points' (or exchanges) of over 400 foods commonly consumed in the UK and an Exchange Diary in which to track their fiber intake to improve understanding, motivation and compliance. In contrast, patients in the control group were counseled at their enrollment interview to maintain their normal (habitual) diet throughout radiotherapy treatment and not to adjust their fiber intake. However they still had the same number of study visits and access to the research team. Educational or recording materials were not provided to the control group. Patients in all groups had access to the research dietician throughout the study to answer *ad hoc* study-related dietary or nutritional queries. The duration of each face-to-face interview

during the study was recorded and median contact time per interview compared between study groups.

Outcome measurements

Gastrointestinal toxicity was assessed as severity of bowel symptoms experienced during the acute (baseline to 5-7 weeks) and chronic (1 year following completion of radiotherapy) period. Symptoms were assessed using the Inflammatory Bowel Disease questionnaire – bowel subset (IBDQ-B) which has been validated in the radiotherapy setting (4). The 32-question IBDQ is a quality of life instrument originally developed for patients with Inflammatory Bowel Disease (18). A maximum score of 224 and minimum of 32 can be obtained with lower scores indicating most severe symptoms. The 10-question (embedded) IBDQ-B has a maximum score of 70 and minimum of 10, once again lower scores indicative of more severe symptoms.

The IBDQ and IBDQ-B scores were obtained at baseline, immediately prior to commencing radiotherapy and thereafter weekly during the 5-7 weeks of radiotherapy and one year after delivery of last radiotherapy session. Data was analyzed as absolute values for nadir (worst) score, end of radiotherapy (acute) and one year after the final radiotherapy (chronic), as well as change in values from baseline to each of these time-points. Total acute bowel symptom burden, as a predictor of chronic burden (19) was examined by computing IBDQ-B area under the curve (AUC) in patients with at least 4 consecutive acute scores. The primary outcome was the difference between study groups in the change in IBDQ-B between baseline and nadir score during radiotherapy.

Other gastrointestinal outcomes included stool form (consistency) and frequency (output). Patients were instructed in the completion of daily self-reported stool diaries

which included the Bristol Stool Form Scale (20) for the assessment of stool form, starting on the day following their enrollment interview through to their exit interview covering their entire radiotherapy treatment period. Mean weekly stool frequency, stool form, number of days on which stools of type 6/7 were passed and number of days on which anti-diarrheal medication was used were compared between groups during week 1, week 4 and the final week of radiotherapy.

Stool SCFA concentrations were measured, to investigate the effect of fiber intake on these, and to explore whether they may be protective mechanisms in preventing radiation-induced gastrointestinal toxicity. Stool samples were collected from patients on day 1 and final day of radiotherapy and immediately weighed and stored at -80˚C for future analysis of SCFA using gas liquid chromatography. Briefly, SCFA were extracted in a 1:4 dilution of extraction buffer (1% H_2PO_4, 0.1% $HgCl_2$) containing an internal standard (2,2-dimethylbutyric acid) and homogenized (Seward Stomacher 80). The extraction was centrifuged (Beckman GS6R) at 5000g for 20 minutes and the supernatant passed through a 0.2 μm filter. In duplicate, filtered supernatant were injected splitless into a gas liquid chromatography system and analyzed using a chromatogram database (Aligent Technologies, US) to give concentrations of acetic, propionic, butyric, valeric, isobutyric and isovaleric acids in μmol/g wet stool.

All patients completed a 7-day food diary during their first and final week of radiotherapy, prospectively recording all food and fluid consumption. Data was entered into a food composition database (Dietplan v.6 Forestfield Software Ltd., Horsham, Surrey). Fiber intake was recorded as NSP intake per day and absolute and change values were calculated and compared. Compliance with fiber target was defined as

achieving 80% of the target for that group, equating to >14.4 g/d NSP for the high fiber group (target ≥18 g/d); <12.0 g/d NSP for the low fiber group (target ≤10 g/d) and a change of <20% in NSP intake between first and final week for the control group. Body weight and Body Mass Index (BMI) were obtained at baseline and end of radiotherapy and absolute and change values were compared between groups.

Palatability of the intervention diets was assessed at the end of radiotherapy using a 150 mm visual analogue scale with responses ranging from 0mm 'much worse than my normal diet'; 75mm 'no different to my normal diet'; 150mm 'much better than my normal diet'. Impact of following the intervention diets on cost of weekly food bills, time spent shopping and in food preparation was assessed by the study research dietician at the exit interview and is reported descriptively.

Statistical methods

Statistical analysis was performed using SPSS software (v.21) employing the ANOVA method for normally distributed data (e.g. IBDQ-B, total IBDQ scores) or Kruskal Wallis test for non-normally distributed data (e.g. stool frequency) between the three groups. Where significant, intergroup comparisons were compared using a Bonferroni *post hoc* correction. The primary end-point was defined as the change in IBDQ-B score between start of radiotherapy and nadir score during the radiotherapy period (acute). This was analyzed by intention to treat (ITT) and per protocol methods. For ITT analysis, missing baseline scores were imputed by carrying backward the first available score, and missing scores at the end of radiotherapy or one year were imputed using last value carried forward. Missing scores during treatment were imputed by taking an average of scores either side of those missing. Data from patients who withdrew from the trial before commencing the intervention was excluded from the analysis. Data from

patients who withdrew during the intervention but consented to allow their data to be included was included in the ITT analysis. Per protocol analysis was performed using scores from patients who achieved ≥80% compliance with fiber target, assessed from the 7-day food diary for the last week of treatment. Results of these analyses were considered significant if $p<0.05$ (ANOVA) in which case post-hoc analysis was undertaken.

The sample size calculation was based on a previous nutrition intervention study with a similar design employing the IBDQ-B as the primary end-point (21). It was calculated that 156 patients were required (52 per group) to detect a difference in the change in IBDQ-B score of ≥6 points between groups from start of radiotherapy to nadir score during treatment, with a significance level of 0.02 (allowing for multiple comparisons) and power of 90%.

Results

Patients

Recruitment took place between December 2009 and December 2013 and was closed when accrual reached n=166, with 10 additional patients recruited to allow for withdrawals. The final trial measurement (1 year follow-up) was obtained in January 2015. **Figure 1** outlines study accrual. Of the 583 eligible patients, 417 declined representing a recruitment rate of 28%. The major reason for declining study enrollment was reluctance to adopt a possible change in diet (36% of patients).

Seven patients withdrew: two declined to commence the study immediately following randomization (low fiber group); two had a stoma placed before radiotherapy (control: 1, high fiber: 1); two were hospitalized during treatment and requested withdrawal (control: 1, low fiber: 1) and one had a change in treatment plan and did not receive radiotherapy (high fiber). A total of 161 patients comprised the ITT population as follows: completed the intervention (n=159); withdrew part-way through the study but consented to their data being included (n=2). Four adverse events occurred all of which were hospital admission for symptom control. None of these were considered related in any way to the study intervention. There were no significant differences in baseline characteristics between groups (**Table 1**).

A total of 644 face-to-face interviews with patients were conducted by the study dietician. Median contact time per interview was not significantly different between groups (p=0.161) and amounted to: 16 minutes for the control group (min: 11, max: 36), 18 minutes (min: 9, max: 31) for the low fiber group and 18 minutes (min: 10, max: 34 mins) for the high fiber group.

Inflammatory Bowel Disease Questionnaire – Bowel subset

IBDQ-B scores were obtained weekly for all patients. The number of missing scores for weeks 1 to 6 and one year post-RT was: 1, 5, 7, 10, 17, 9 and 35 respectively. Raw scores and comparisons between groups at all time points are shown in **Table 2**. There were no differences in IBDQ-B scores at baseline between the three groups. Overall, IBDQ-B scores decreased in all groups during treatment, indicative of worsening bowel symptoms. In the ITT population, there was no significant difference between groups in the change in score between baseline (start of radiotherapy) and nadir score during treatment (primary endpoint, p=0.093).

There was no differences in absolute IBDQ-B scores at the end of radiotherapy between the three groups, however, there was a significant difference in the between group change scores between baseline and final week of radiotherapy (p=0.014) (**Figure 2**). Post hoc analysis revealed a smaller reduction in score in the high fiber group (-3.7, SD 12.8) compared with control group (-10.8, SD 13.5), a clinically significant difference of -7.1 points (95% CI -12.99 : -1.27) (p=0.011). However, the change in score was not significantly different between the low fiber group (-7.9, SD 11.3) and control (p=0.711) or between the low fiber and high fiber groups (p=0.251).

The absolute IBDQ-B scores at 1 year post-RT and the change in scores between baseline and 1 year post-RT were significantly different between groups (**Figure 3**). Post hoc analysis revealed that at 1 year following radiotherapy, IBDQ-B scores had returned to baseline values in the high fiber group (+0.1, SD 14.5) compared with a reduction in the control group (-8.4, SD 13.3), a clinically significant difference of -8.5 points (95% CI -14.8 : -2.2) (p=0.004). However, the change in IBDQ-B scores was not significantly different between the low fiber group (-4.9, SD 12.7) and control

(p=0.546) or between the low fiber and high fiber groups (p=0.172) (Table 2).

Per protocol analysis revealed no significance differences between groups in IBDQ-B scores at any time-points or in the change in scores between time-points. However, patient numbers were small with only 128 patients (22 control, 34 low fiber, 27 high fiber) included in the analysis due to limited numbers achieving ≥80% compliance with fiber target.

Computation of IBDQ-B area under the curve (153 patients) showed no significant difference between groups (p=0.576; Kruskal Wallis test, non-parametric data).

Inflammatory Bowel Disease Questionnaire

IBDQ scores were obtained weekly for all patients with missing scores imputed as reported above for IBDQ-B. Raw scores and comparisons between groups at all time points are shown in Table 2. There were no differences in IBDQ scores at baseline between the three groups. Overall, scores decreased in all groups during treatment, indicative of worsening overall symptoms and resulting impaired quality of life. In the ITT population, there was no significant difference between groups in the change in score between baseline (start of radiotherapy) and nadir score during treatment (p=0.203).

There was no difference in absolute IBDQ scores at the end of radiotherapy between the three groups, however, there was a significant difference in the change in score between baseline and final week of radiotherapy (p=0.018) (Figure 2). Post hoc analysis revealed a smaller reduction in score in the high fiber group (-8.2, SD 30.2) compared with control group (-24.5, SD 32.0), a clinically significant difference of -16.2 points (95%

CI -30.12 : -2.46) (p=0.018). However, the change in score was not significantly different between the low fiber group and control (p=0.708) nor between the low fiber and high fiber groups (p=0.303).

The absolute IBDQ scores at 1 year post-RT (p=0.001) and the change in scores between baseline and 1 year post-RT (Figure 3) were significantly different between groups (p<0.001). Post hoc analysis revealed that at 1 year following radiotherapy, IBDQ scores had returned to exceed baseline values marginally in the high fiber group (+2.1, SD 29.4) compared with a reduction in the control group (-21.4, SD 33.0), a difference of -23.8 points (95% CI -38.2 : -9.3) (p<0.001). The change in IBDQ scores was also significantly different between the low (-13.23, SD 30.3) and high fiber groups (p=0.030) but not between the low fiber and control groups (p=0.530) (Table 2).

Per protocol analysis (n=22 control, n=34 low fiber, n=27 high fiber) revealed a significant difference between groups in IBDQ scores at 1 year post-RT (p=0.030). Post hoc analysis revealed a significant difference of 20.4 points (95% CI 1.9 : 38.9) (p=0.026) between the high fiber and control groups (Table 2). However, there were no differences between groups in the change in IBDQ score between any time-points.

Stool frequency and form

Stool diaries were returned by 125 (78%) patients, (44/54 control group; 39/53 low fiber; 42/54 high fiber). There were no significant differences in stool frequency or stool form during week 1 (start of radiotherapy) or the final week (end of radiotherapy) between any of the three groups, nor was there a difference in the number of days during which patients experienced a stool form of 6 or 7 (loose or watery stools) or the number of days on which anti-diarrheal medication was taken (**Table 3).**

Short-chain fatty acids

In an exploratory analysis, paired stool samples were provided by a sub-group of 41 patients at baseline and end-RT (control group: 16, low fiber: 15, high fiber: 10). No significant differences were found between groups in total SCFA concentrations either at baseline or end-RT (**Table S2**).

Nutritional data

The number of 7-day food diaries returned was 146 (91%) at baseline (51 control group, 47 low fiber, 48 high fiber) and 139 (86%) during the final week of RT (44 control group, 41 low fiber, 43 high fiber). During week 1 of radiotherapy, following dietary advice, there was a significant difference in fiber intake between groups ($p<0.001$: ANOVA) which was also apparent during the final week of radiotherapy ($p<0.001$: ANOVA), all in line with group allocations (low fiber < control < high fiber) (**Table 4**). A significant difference was observed in protein intake (g/d) between groups during the final week of radiotherapy ($p=0.012$). Post hoc analysis showed a mean difference of 14.6 g/day between the low and high fiber groups (68.6, SD 24.5 *vs* 78.4, SD 22.7, $p=0.012$). However, there were no differences between groups in other macronutrient intakes (fat and carbohydrates) at week 1 or final week of radiotherapy.

Using paired data (food diaries returned at both time-points) significant within-group reductions were seen in total energy, protein and fat intake in the control and low fiber groups (**Table 5**). In contrast no significant differences in nutrient intake were observed in the high fiber group.

There were no significant differences in body weight or BMI at either baseline or end of RT, nor in changes in these values, between the three groups (Table 4).

Of the 40/53 (75%) patients in the low fiber group and 38/54 (70%) in the high fiber group who completed the palatability questionnaires, there was no significant difference in perceived palatability of the low (median 78.5 (min 7 – max 146) mm) *vs* high fiber diets (78.0 (5 – 150)).

There was little difference between the high and low fiber groups with respect to the impact of the study diet. A total of 64% of patients in the low fiber *vs* 59% in the high fiber group reported that the study diet had a minimal effect, or had reduced the cost of their weekly food bills; 60% of patients in the low fiber group *vs* 58% in the high fiber group reported that the study diet had no impact, or reduced time spent shopping and 64% of patients in the low fiber *vs* 56% in the high fiber group reported that the study diet had no effect, or had reduced food preparation time. No response: 27% low fiber, 34%, high fiber groups.

Discussion

This is the first randomized controlled trial (RCT) designed to test the efficacy of manipulating dietary fiber in patients receiving radical pelvic radiotherapy. Whilst no significant difference between groups was found in the primary outcome (change in IBDQ-B between baseline and nadir score), the results revealed a clinically significant difference in change score of 7.1 points (p=0.011) between the high fiber and control groups, between start and end-RT, pointing to a clear benefit of increased fiber intake. The fact that at 1 year post-RT, the difference in score between these groups was 8.5 points (p=0.004) indicating a longer term effect, fits with current concepts of radiotherapy toxicity that encompass the consequential effect (22), namely that severe acute toxicity predisposes to longer term severe toxicity. These differences between groups in the change in IBDQ-B score is equivalent to a ≥10% change, which has previously been defined as 'meaningful clinical improvement' (23). It should be noted that despite these results, we did not show a gradient of effect. IBDQ-B scores in the low fiber group were higher (less severe symptoms) at both time-points compared to the control group, albeit not statistically significantly, indicating a possible benefit. The analysis of IBDQ (quality-of-life) scores revealed a similar pattern, with the high fiber group maintaining significantly improved scores compared to the control group at end-RT (p=0.018) and at 1 year (p=<0.001).

Conducting robust, large scale nutritional interventions requiring patients to adhere to targets and estimate intake are labour-intensive and far from straightforward. We set fiber targets based on the NSP content of foods to ensure compatibility with Dietary Reference Values in the UK at the time (24) and provided a bespoke booklet for patients to readily track their intake. Patients were coached to use this booklet rather than food

labels as their prime reference source and were given diaries in which to record daily self-estimated fiber consumption. In the UK, food labelling is based on the US Association of Official Analytical Chemists (AOAC) method of analysis which yields values 1.6 x NSP/100g food. Despite these potential pitfalls, we are confident in the validity of our findings since a clear differential in fiber intake was maintained between groups during the first and final week of treatment ($p<0.001$ both time-points). Most patients (85%) reported they found the booklets very easy to use and would recommend them to others wishing to track their fiber intake.

Importantly, our findings challenge non-evidence based advice to restrict dietary fiber during radical pelvic radiotherapy. Analysis of stool frequency, form and number of days on which loose / watery stools was experienced showed no significant differences between groups in any of these characteristics. Thus, the premise that increased fiber exacerbates a tendency towards treatment-induced diarrhea appears to lack physiological foundation. On the contrary, optimal production of SCFA by bowel microbiota provided with ample fiber substrate would encourage sodium and water absorption (12) and thus help to counteract risk of loose or watery stool. In addition to promoting water absorption, we hypothesized that increased fiber intake would enhance SCFA production which in turn would reduce inflammatory processes thereby mitigating symptoms as reflected in IBDQ-B scores. However, we found no difference between groups. This may be due to the small number of samples we obtained, the wide inter-individual variations in stool SCFA concentrations that exist (25) and altered gut transit time during treatment (26, 27) which has a large effect on stool SCFA concentrations. Further studies are needed to explore our hypothesis.

Our interventions had no adverse effect on body weight, BMI or total energy intake. Although all of these parameters decreased in all groups between baseline and end-RT, no significant differences between groups occurred. Within group analysis revealed no significant change in total energy or macronutrient intake in the high fiber group, a finding in keeping with recent research which challenges the long-held view that fiber leads to increased satiety and causes reduced energy intake (28, 29). However, significant within-group reductions in protein, fat and total energy intake occurred in the control and low fiber groups between baseline and end-RT. We cannot determine whether maintenance of total energy intake in the high fiber group contributed to their improved quality-of-life (IBDQ) scores or vice-versa although others have reported an association (30, 31).

We recognize that there are a number of factors that could have confounded our results. First, there was considerable attrition at 1 year requiring imputation for ITT analysis. However, the control group who reported the worst bowel symptoms in the acute setting also went on to experience the worst symptoms at 1 year post-RT which fits with previous research (5, 22). Secondly, treatment-related factors were balanced between groups at baseline. However, patient-related factors such as smoking history, inflammatory conditions and previous surgery all of which confer an adverse effect and in contrast, the use of anti-hypertensive medication and/or HMG CoA reductase inhibitors which confer a protective effect (32) and could have influenced outcomes, were not captured. Thirdly, cytotoxic agents (anti-metabolite Capecitabine and alkylating agents Mitomycin C and Cisplatin) and/or non-cancer related medications, may cause gastrointestinal symptoms in their own right through inflammatory or other

mechanisms and thus may exacerbate symptoms and overwhelm potentially protective nutritional agents.

We conclude that individualized dietetic advice to follow a high fiber diet during pelvic radiotherapy was tolerable and resulted in reduced gastrointestinal toxicity both acutely at the end of radiotherapy and at one year after radiotherapy compared with habitual fiber intake. We note that a low fiber diet also appeared to confer some benefit and may offer a degree of advantage via different mechanisms. However, we agree with others in that a critical objective for dietetic practice is that ineffective, unnecessary or restrictive practices that lack an evidence-base and yet place undue burden on patients are abandoned (31) and thus our recommendation is that advice to reduce fiber intake during pelvic radiotherapy be discarded.

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Table 1 - Baseline characteristics of randomized patients

Characteristic	**All groups n=166**	**Control n=55**	**Low Fiber n=55**	**High Fiber n=56**	**P value**
Age: years	62.5	63	62	64	0.959*
Median	(26 – 91)	(35 – 88)	(26 – 91)	(28 – 87)	
(min-max)					
Gender: n (%)					0.580**
Male	70 (42)	23 (42)	26 (47)	21 (37)	
Female	96 (58)	32 (58)	29 (53)	35 (63)	
Pelvic site: n (%)					0.948**
Gastrointestinal	106 (64)	35 (64)	36 (65)	35 (63)	
Colorectal	80 (75)	27 (76)	27 (76)	26 (74)	
Anal	26 (25)	8 (23)	9 (25.5)	9 (25.5)	
Gynecological	60 (36)	20 (36)	19 (35)	21 (37)	
Endometrial	36 (60)	13 (65)	14 (74)	9 (43)	
Cervical	20 (33)	4 (20)	5 (26)	11 (52)	
Vaginal	3 (5)	2 (10)	0	1 (5)	
Vulval	1 (2)	1 (5)	0	0	
Concomitant CT: n (%)	121 (72)	38 (69)	41 (75)	42 (75)	0.739**
RT dose (Gy):	50.4	52.2	50.4	50.4	0.398*
Median	(30.0 –	(45.0 –	(30.0 – 59.4)	(45.0 –	
(min-max)	70.0)	70.0)		69.6)	

Key: CT: chemotherapy; *Kruskal-Wallis' test; **Chi-squared test

Table 2 - Summary of IBDQ-B and IBDQ scores between the three groups in the intention to treat population

	Control n=54	**Low fiber** n=53	**High fiber** n=54	***ANOVA p value***
IBDQ-B scores (absolute values)				
Baseline (start of RT)	64.1 (6.9)	63.9 (9.3)	61.7 (9.7)	0.273
End of RT	53.3 (13.2)	56.0 (10.7)	58.0 (10.2)	0.104
Nadir (lowest score) during RT	48.7 (12.8)	52.2 (10.5)	51.5 (11.6)	0.260
One year post-RT	55.7 (11.5)	59.0 (10.9)	61.8 (11.8)	**0.024**[1]
Change from baseline in IBDQ-B scores				
End RT	-10.8 (13.5)	-7.9 (11.3)	-3.7 (12.8)	**0.014**[2]
Nadir (lowest score) during RT	-15.5 (13.2)	-11.8 (10.6)	-10.2 (13.7)	0.093
One year post-RT	-8.4 (13.3)	-4.9 (12.7)	0.1 (14.5)	**0.005**[3]
IBDQ scores				
Start of RT (baseline)	194.4 (17.9)	196.3 (23.7)	191.7 (26.0)	0.566
End of RT	170.5 (33.4)	178.6 (26.6)	183.5 (28.1)	0.073
Nadir (lowest score) during RT	161.5 (33.6)	171.3 (28.0)	168.0 (32.0)	0.259
One year post-RT	173.6 (32.0)	183.0 (26.8)	194.1 (23.1)	**0.001**[4]
Change from baseline in IBDQ scores				
End RT	-24.5 (32.0)	-17.7 (26.2)	-8.2 (30.2)	**0.018**[5]
Nadir (lowest score) during RT	-33.4 (31.6)	-25.9 (27.2)	-23.7 (33.2)	0.203
One year post-RT	-21.4 (33.0)	-13.23 (30.3)	2.14 (29.4)	**<0.001**[6]

Negative values represent a fall in score (worsening symptoms)
Bold type indicates significant at $p<0.05$ following ANOVA.
Where values are statistically significant a Bonferroni post hoc correction was undertaken, superscripts indicate significant differences between groups as follows: 1: High fiber *vs* control group ($p=0.019$); 2: High fiber *vs* control group ($p=0.011$); 3: High fiber *vs* control group ($p=0.004$); 4: High fiber *vs* control group ($p<0.001$); 5: High fiber *vs* control group ($p=0.015$); 6: High fiber *vs* control group ($p<0.001$), high fiber and low fiber group ($p=0.030$)

Table 3 - Summary of stool characteristics between groups in patients with completed stool charts

	Control n=44	**Low fiber** n=39	**High fiber** n=42	***p value****
Stool frequency, median (min-max), stool/d				
Week 1 (start of RT)	1.9 (0.4 – 6.7)	1.7 (0.7 – 12.1)	2.0 (0.7 – 13.9)	0.797
Final week (end of RT)	3.0 (0.3 – 13.5)	2.7 (0.6 – 11.0)	2.3 (0.9 – 13.8)	0.636
Stool form, median (min-max)				
Week 1 (start of RT)	4.7 (2.0 – 6.4)	5.0 (2.4 – 6.6)	4.9 (1.8 – 6.6)	0.630
Final week (end of RT)	4.8 (2.5 – 6.8)	5.2 (3.9 – 7.0)	5.1 (3.0 – 6.6)	0.225
No. days with stool type 6 or 7, median (max-min)				
Week 1 (start of RT)	2 (0 – 7)	3 (0 - 7)	2 (0 – 7)	0.627
Final week (end of RT)	3.0 (0 – 7)	3.0 (0 – 7)	3.0 (0 – 7)	0.934
No. of medication days, median (max-min)				
Week 1 (start of RT)	0 (0 – 7)	0 (0 – 7)	0 (0 – 2)	0.713
Final week (end of RT)	0 (0 – 7)	0 (0 – 7)	0 (0 – 7)	0.515

Key: * Kruskal Wallis test

Table 4 - Summary of nutritional intake and anthropometry between the three groups in the intention to treat population

	Control n=54	**Low fiber** n=53	**High fiber** n=54	***p value***
Fibre, g/d NSP, mean (SD)				
Week 1 (start of RT)	13.6 (5.3)	10.2 (3.4)	17.1 (4.8)	**<0.001**[1]
Final week (end of RT)	12.2 (5.2)	8.9 (3.0)	15.7 (5.1)	**<0.001**[2]
At least 80% compliant with fiber target at final week (end of RT) n (%)				
Final week (end of RT)	22/44 (50%)	34/41 (83%)	27/43 (63%)	**0.006***
Energy intake, kcal/d, mean (SD)				
Week 1 (start of RT)	1883 (561)	1693 (415)	1898 (524)	0.134
Final week (end of RT	1715 (569)	1571 (496)	1836 (453)	0.062
Body weight, kg, mean (SD)				
Week 1 (start of RT)	81.0 (18.5)	78.3 (18.1)	77.5 (15.6)	0.559
Final week (end of RT)	81.0 (18.0)	78.1 (17.9)	76.6 (16.6)	0.433
Body mass index, kg/m2, mean (SD)				
Week 1 (start of RT)	28.4 (6.3)	27.8 (5.8)	28.0 (5.4)	0.880
Final week (end of RT)	28.6 (6.4)	26.8 (5.0)	27.5 (5.4)	0.291

Bold type indicates significant at $p<0.05$ following ANOVA (superscript), or * Chi-squared test
Where values are statistically significant a Bonferroni post hoc correction was undertaken, superscripts indicate significant differences between groups as follows:
1: Control vs low fiber group ($p=0.019$), control vs high fiber group ($p=0.001$), low fiber vs high fiber group ($p<0.001$); 2: Control vs low fiber group ($p=0.003$), control vs high fiber group ($p=0.001$), low fiber vs high fiber group ($p<0.001$)

Table 5 - Summary of within group changes in nutritional intake in patients with evaluable data at week 1 and final week of radiotherapy

	Control n=44	Low fiber n=41	High fiber n=42
Protein, g/d NSP, mean (SD)			
Week 1 (start of RT)	76.0 (21.6)	72.3 (17.2)	80.2 (21.1)
Final week (end of RT)	68.3 (24.5)	63.8 (19.8)	78.3 (23.0)
Significance (paired t-test)	**0.006**	**0.002**	0.479
Fat, g/d, mean (SD)			
Week 1 (start of RT)	74.2 (27.5)	71.4 (25.6)	77.7 (27.6)
Final week (end of RT)	65.9 (24.5)	63.2 (22.8)	73.3 (23.4)
Significance (paired t-test)	**0.016**	**0.014**	0.249
CHO (carbohydrates), g/d, mean (SD)			
Week 1 (start of RT)	210.6 (71.9)	186.0 (49.0)	221.0 (65.4)
Final week (end of RT	197.2 (72.8)	178.5 (66.1)	206.0 (57.9)
Significance (paired t-test)	0.073	0.345	0.084
Energy, kcal/d, mean (SD)			
Week 1 (start of RT)	1886 (554)	1717 (425)	1944 (540)
Final week (end of RT)	1715 (569)	1571 (496)	1834 (458)
Significance (paired t-test)	**0.010**	**0.019**	0.132

Bold type indicates significant at $p<0.05$

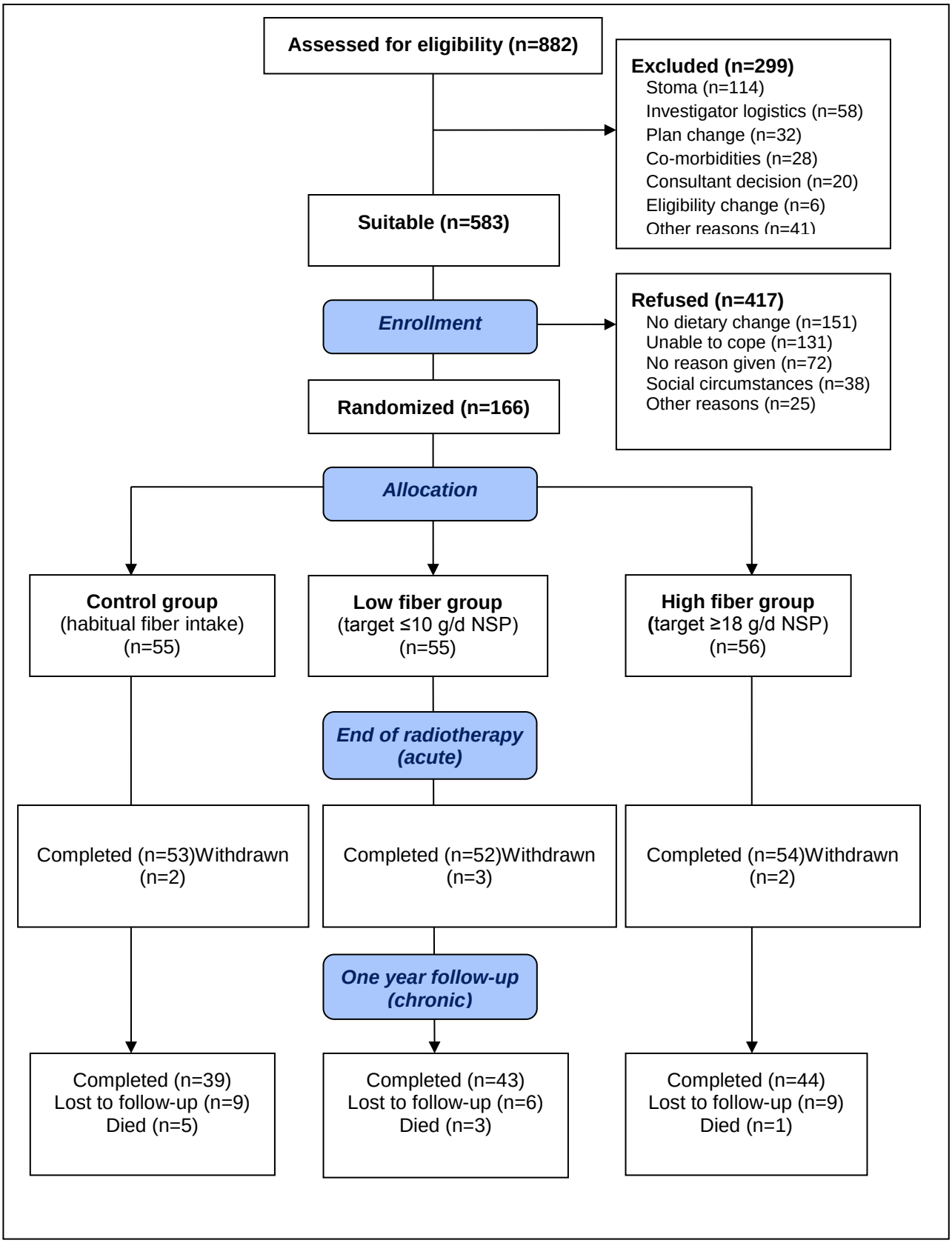
Figure 1 - CONSORT style flowchart of patient accrual

Key: NSP: Non-starch polysaccharide

Figure 2 – Mean change in IBDQ-B scores (points) during treatment with 95% CIs

Figure 3 – Mean change in IBDQ-B scores (points) 1 year after treatment with 95% CIs

Figure 1 - CONSORT style flowchart of patient accrual



Key: NSP: Non-starch polysaccharide

Figure 2 – Mean change in IBDQ-B scores (points) during treatment with 95% CIs

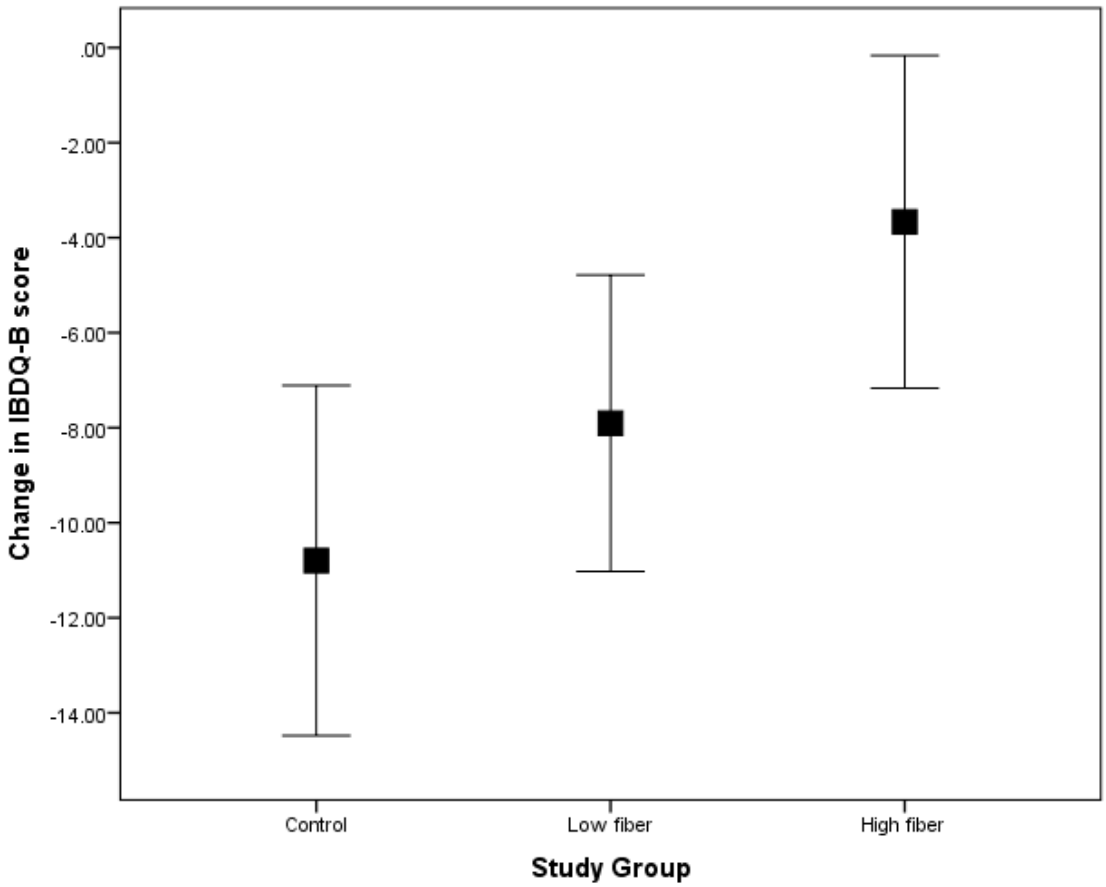


Figure 3 – Mean change in IBDQ-B scores (points) 1 year after treatment with 95% CIs