Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial

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Summary

Background Chronic gastrointestinal symptoms after pelvic radiotherapy are common, multifactorial in cause, and affect patients' quality of life. We assessed whether such patients could be helped if a practitioner followed an investigative and management algorithm, and whether outcomes differed by whether a nurse or a gastroenterologist led this algorithm-based care.

Methods For this three-arm randomised controlled trial we recruited patients (aged ≥18 years) from clinics in London, UK, with new-onset gastrointestinal symptoms persisting 6 months after pelvic radiotherapy. Using a computer-generated randomisation sequence, we randomly allocated patients to one of three groups (1:1:1; stratified by tumour site [urological, gynaecological, or gastrointestinal], and degree of bowel dysfunction [IBDQ-B score <60 *vs* 60–70]): usual care (a detailed self-help booklet), gastroenterologist-led algorithm-based treatment, or nurse-led algorithm-based treatment. The primary endpoint was change in Inflammatory Bowel Disease Questionnaire–Bowel subset score (IBDQ-B) at 6 months, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00737230.

Findings Between Nov 26, 2007, and Dec 12, 2011, we enrolled and randomly allocated 218 patients to treatment: 80 to the nurse group, 70 to the gastroenterologist group, and 68 to the booklet group (figure). Most had a baseline IBDQ-B score indicating moderate-to-severe symptoms. We recorded the following pair-wise mean difference in change in IBDQ-B score between groups: nurse versus booklet 4·12 (95% CI 0·04–8·19; p=0·04), gastroenterologist versus booklet 5·47 (1·14–9·81; p=0·01). Outcomes in the nurse group were not inferior to outcomes in the gastroenterologist group (mean difference 1·36, one sided 95% CI –1·48).

Interpretation Patients given targeted intervention following a detailed clinical algorithm had better improvements in radiotherapy-induced gastrointestinal symptoms than did patients given usual care. Our findings suggest that, for most patients, this algorithm-based care can be given by a trained nurse.

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See **Online** for a video interview with Jervoise Andreyev

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Introduction

The number people who survive cancer has tripled in the past 30 years.[1] However, chronic physical consequences of treatment for cancer adversely affect on the quality of life of 20–25% of survivors.[2]

The largest group of patients reporting debilitating chronic side-effects are those treated with radiotherapy alone or in combination with other treatments for pelvic cancer. Gastrointestinal symptoms are the most common chronic physical side-effects and have the greatest effect on daily activity.[3,4] Overall, 50% of patients report that their gastrointestinal symptoms affect their quality of life and 20–40% say that this effect is moderate or severe.[5] Such problems include chronic faecal incontinence (up to 60% of patients) after radiotherapy for prostate or rectal cancer,[6,7] and chronic loose stool (47%), defaecatory urgency (29%), or chronic abdominal pain (17%) after radiotherapy for gynaecological cancer.[8]

In 2010, the UK National Cancer Survivorship Initiative Vision challenged professionals to develop new models of care for these patients because "the needs of cancer survivors are not being met, that being 'cured' of cancer does not necessarily equate with being well and that chronic consequences of treatment can have a devastating impact on daily life".[9]

To meet the challenge of the survivorship initiative and to develop a sustainable service to deal with the rapidly escalating demand for treatment, we explored the potential of nurse-delivered, algorithm-directed care for these patients.

Radiotherapy induces long-term changes in bowel function as a result of progressive endothelial dysfunction, which induces ischaemia and subsequent fibrosis. The same processes might cause dysfunction in other pelvic organs, a disorder defined as pelvic radiation disease.[10] During therapeutic irradiation of a cancer in the pelvis, parts of distal small bowel, caecum, transverse and sigmoid colon, and rectum are often also irradiated. Additionally, the pancreas and proximal small bowel might also receive some irradiation if para-aortic nodes are treated. That even low dose radiation can cause substantial changes to gastrointestinal function is becoming increasingly recognised.[11]

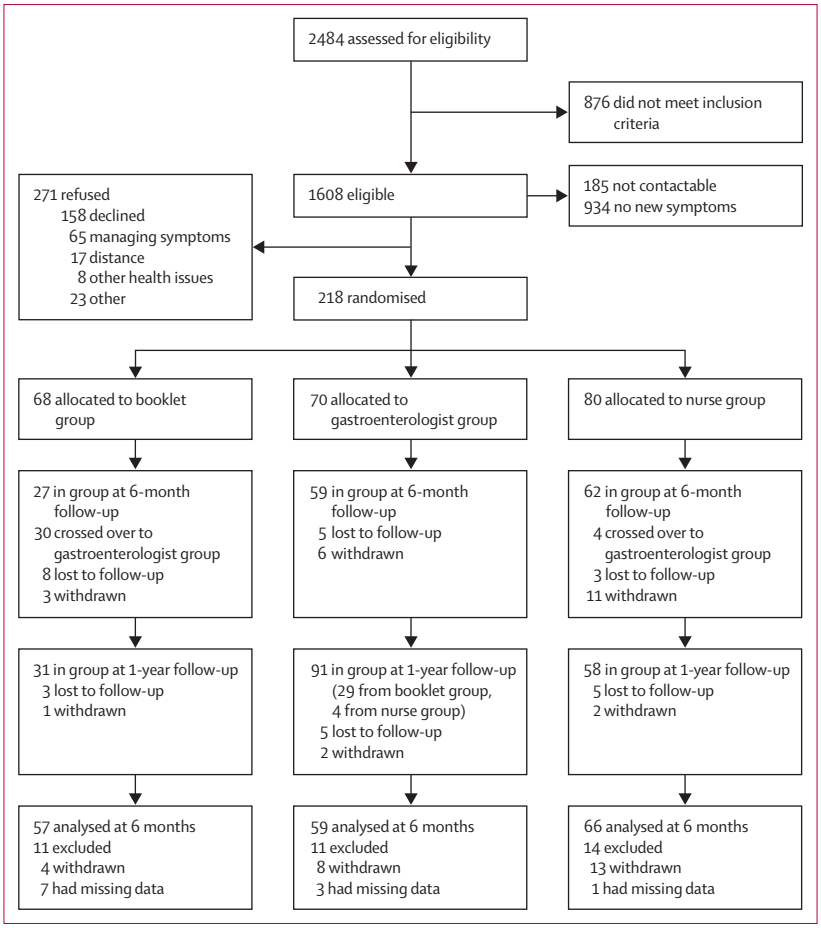

Figure: **Trial profile**

We know of no previous clinical trials investigating whether radiation-induced bowel injury is treatable, but a substantial amount of clinical research challenges the widely held view that nothing can be done to manage these patients' symptoms.[12,13] This research indicates that gastrointestinal symptoms arise because irradiation potentially induces a variety of abnormalities in physiological functioning in exposed areas of the gastrointestinal tract. Changes in different physiological functions can result in identical symptoms, so the presence of a specific symptom or cluster of symptoms does not predict the underlying cause.[14,15] Because more than one gastrointestinal physiological function is often affected, patients' symptoms could have more than one cause.

We postulated that when a patient develops new gastrointestinal symptoms after pelvic irradiation, systematic assessment should be able to identify which physiological abnormalities are contributing to these symptoms. If abnormalities are detected, then treatments prescribed to treat each abnormality systematically should be effective.

In a series of studies,[16–18] we identified 23 symptoms that develop after radiotherapy. We defined the investigations needed to find out the cause or causes of each symptom and possible sequential treatments. We piloted and adjusted the resultant algorithm in our clinic.[16–18] After adjustment, the algorithm provides a step-by-step approach along a care pathway from initial identification of symptoms to long-term management. We previously showed that our algorithm could be applied by a nurse and that it seemed to improve symptoms.[19]

We tested whether patients with new-onset gastrointestinal symptoms after previous pelvic radiotherapy could be helped if a practitioner followed our investigative and management algorithm, and whether a nurse could apply the algorithm in such a way that outcomes were not worse than when applied by a consultant gastroenterologist.

Methods

Participants and trial design

Optimising Radiotherapy Bowel Injury Therapy (ORBIT) was a single centre, prospective, three-arm, non-blinded, randomised, controlled trial. We recruited patients (aged ≥18 years) who had troublesome, persisting gastrointestinal symptoms that started during or after radiotherapy given with curative intent for histologically proven prostatic, bladder, vulval, vaginal, cervical, endometrial, anal, or rectal malignant neoplasia or paraaortic irradiation for metastatic disease from any of those primary sites or the testis. Radiotherapy should have been completed at least 6 months before enrolment. Patients needed to travel to The Royal Marsden Hospital (London, UK) and be well enough to be managed as out-patients. Patients were excluded if they needed immediate gastroenterological assessment, had a colostomy or ileostomy (these patients became eligible 6 months after stoma reversal), had previously seen a gastrointestinal specialist for these symptoms, had metastatic disease, serious comorbidity, or a life expectancy of less than 1 year. If a patient had a recurrence of cancer requiring treatment or was admitted to hospital for gastrointestinal symptoms, they were withdrawn from the study.

We identified potentially eligible patients from a list generated by the radiotherapy unit at our hospital. They were recruited directly from follow-up clinics, or contacted by mail or telephone. Additionally, patients referred to our clinic on a non-urgent basis were, if eligible, invited to enrol. Suitability of patients with symptoms who had not been previously referred to our clinic was confirmed with their oncologist before randomisation.

This trial was approved by the local Institutional Research and Development and Ethics Committees. Trial progress was monitored by a steering group that met quarterly and included patient representatives. All patients provided written consent.

Trial design

Participating patients were randomly allocated to one of three groups: usual care (a detailed self-help booklet),[20,21]

managed according to the algorithm by a consultant gastroenterologist, or managed according to the algorithm by a specially trained research nurse.[19] Patients in the booklet group whose symptoms continued 6 months after recruitment were offered consultation with the gastroenterologist and, if appropriate, investigation and treatment. Patients in the nurse-led care group were crossed over to the gastroenterologist-led care group if they had gastrointestinal issues that were beyond the scope of the algorithm.

Randomisation and masking

Using a computer-generated randomisation sequence and random permuted blocks, we allocated patients (1:1:1; stratified by tumour site [urological, gynaecological, or gastrointestinal], and degree of bowel dysfunction [IBDQ-B score <60 *vs* 60–70) to one of the three groups. The randomisation office of the Institute of Cancer Research (Sutton, UK), which had no further involvment in the trial, generated the randomisation sequence only after written consent to enter the trial had been obtained and eligibility had been checked by the independent study monitor.

Assessments

Patients were assessed at recruitment and at 6 months and 1 year after randomisation. The primary endpoint was improvement in gastrointestinal symptoms, measured with the Modified Inflammatory Bowel Disease Questionnaire bowel subset score (IBDQ-B). The IBDQ was developed for use in monitoring disease activity and quality of life in Ulcerative Colitis and Crohn's Disease.[22] It has been validated in Crohn's Disease in primary, secondary, and tertiary care, and in different ethnic groups. The modified IBDQ and IBDQ-B are a simpler, more sensitive measure of quality of life and radiation-induced gastrointestinal symptomatology than two widely used toxicity scales, Radiation Therapy Oncology Group Toxicity scale (RTOG) and Late Effects of Normal Tissues (LENT) Subjective-Objective Management Analytic (SOMA) scales.[17,23] Secondary endpoints were the effect of intervention on quality of life, anxiety and depression scores, and pelvic symptom scores. We recorded patient characteristics and oncological treatment details at the first visit. Bowel function was further assessed using the St Mark's Faecal Incontinence score[24] and LENT SOMA score.[25] We assessed sexual function in men using International Continence Society – sex questionnaire (ICSsex)[26] and urinary function using ICSmaleSF.[26] For women, the equivalent questionnaires were Jensen Q[27] and Bristol Female Lower Urinary Tract Symptoms Questionnaire (BFLUTSQ).[28] We assessed anxiety and depression using hospital anxiety and depression scale (HAD)[26] and general functioning using aork and social adjustment scale (WASA).[29] We used SF-12 (version 1) to measure generic health-related quality of life[30] and for later calculation of quality-adjusted life years (QALYs).[31]

Statistical analysis

The primary endpoint in the study was difference in IBDQ-B score 6 months after randomisation. On the basis of findings from a previous study,[23] we calculated that the mean acute change in IBDQ-B scores of patients after 5 weeks of radiotherapy was –7·4 (SD 9·2). In other ongoing studies from patients attending our clinic with late consequences of treatment, we were able to derive a point estimate which suggested that the mean score was similar (61·6 *vs* 59·0 [SD 9·9]).

We aimed to detect differences between use of the booklet and use of the intervention (the gastroenterologist and nurse groups combined) and to assess for non-inferiority between nurse and gastroenterologist delivered care. A change in score of 6 or more in the IBDQ-B is a clinically relevant difference from a patient perspective.[32] We assumed therefore that a difference in change between the two algorithm arms of 4 or less could be considered as nurse-led management not being worse than gastroenterologist-led management.

To achieve 80% power with an SD of 9·2 and a one-sided test at 5% significance level to allow comparison between standard care versus intervention, we needed a total of 60 assessable patients in each group. To assess non-inferiority between the gastroenterologist and nurse groups, we needed a further ten assessable patients (ie, 70 patients) in both the gastroenterologist and nurse groups. Assuming a 9% drop-out rate for the whole study, 196 patients were needed for the initial randomisation to all three groups. After these patients had been enrolled, the booklet group would close and recruitment of 22 more patients to the two intervention groups only would continue until 218 patients in total were randomly allocated. The significance level did not need to be adjusted for multiple testing because it was separate from the comparison, which was to show superiority. We used descriptive statistics and examined differences from baseline using non-parametric methods. The study was analysed on an intention-to-treat basis. We used IBM SPSS (version 21) for all statistical analyses.

This trial is registered with ClinicalTrials.gov, number NCT00737230.

Results

We began enrolment on Nov 26, 2007. The trial was suspended for 5 months from Sept 2, 2008, to Feb 14, 2009, after a fire disrupted clinical services. The booklet group was closed after randomisation of 196 patients on June 14, 2011. Recruitment of 218 patients was completed on Dec 12, 2011. Follow-up was completed on Nov 26, 2012.

We randomly enrolled 218 of 2484 screened patients: 80 to the nurse group, 70 to the gastroenterologist group, and 68 to the booklet group (figure). 25 (11%) patients were withdrawn from the study before completion (table 1).

	Numbers of patients withdrawn	Booklet group (n=4)	Gastroenterologist group (n=8)	Nurse group (n=13)
0–6 months	20	Three required hospital admission	Three ineligible patients incorrectly enrolled Two needed hospital admission One had a cancer relapse	Six due to temporary halting of the study Three needed hospital admission One ineligible patient incorrectly enrolled One with gastrointestinal issues not covered by the algorithm
>6 months	5	One had a cancer relapse	Two had a cancer relapse	Two had a cancer relapse

Table 1: **Withdrawal from the ORBIT study after randomisation**

	n	Booklet group (n=68)	Gastroenterologist group (n=70)	Nurse group (n=80)
Men	168	51 (75%)	55 (79%)	62 (77%)
Women	50	17 (25%)	15 (21%)	18 (23%)
Age in years	218	69·5 (37–80)	68·5 (29–87)	67 (34–83)
Men	168	71 (45–80)	70 (49–83)	70 (34–83)
Women	50	59 (37–79)	65 (29–87)	60 (44–79)
Radiotherapy total dose (Gy)	218	64·5 (17–74)	70 (22–100)	60 (25–111)
Months since end of radiotherapy	213	8·0 (4·5–32·0%)	8·2 (5·1–28·5)	8·8 (4·4–30·7)
Original primary tumour site				
Gastrointestinal	28	10 (15%)	5 (7%)	13 (16%)
Gynaecological	34	11 (16%)	12 (17%)	11 (14%)
Urological	156	47 (69%)	53 (76%)	56 (70%)
Previous colorectal surgery				
Yes	11	2 (3%)	3 (4%)	6 (8%)
No	188	59 (87%)	60 (86%)	69 (86%)
Not known	19	7 (10%)	7 (10%)	5 (6%)
Domestic circumstances				
Living alone	46	11 (16%)	15 (21%)	20 (25%)
Married	156	54 (79%)	51 (73%)	51 (64%)
Living with a partner	9	2 (3%)	1 (1%)	6 (7%)
Living with other family	6	1 (2%)	2 (3%)	3 (4%)
Not known (%)	1	0	1 (2%)	0

Data are n (%) or median (range).

Table 2: **Baseline characteristics (intention-to-treat population)**

Most patients were men (table 2). Overall, median age was 68 years, but women were younger (median age 61 years) than men (median 70 years). Women and men treated for gastrointestinal cancer had similar median ages (62 years [range 46–76] for women, 63 years [34–80] for men), but women treated for a gynaecological cancer had a median age of 59 years (29–87) and patients recruited with previous urological cancer were all treated for prostate cancer and were on average older (median age 70 years [34–83]). Baseline characteristics were otherwise much the same between the three treatment groups (table 2).

Of 271 eligible patients who declined to take part, 33 (12%) had been treated for gastrointestinal malignancy, 52 (19%) for a gynaecological tumour, and 189 (69%) for a urological tumour. Each of these three groups had a median age older (2–5 years) than those participating.

Two-thirds of patients had an IBDQ-B score below 60, indicating moderate or severe symptoms (table 3). Mean improvement in IBDQ-B score at 6 months in the booklet group was 4·9 (SD 13·2; 95% CI 1·4–8·4), but the magnitude of this change is not considered clinically significant. By contrast with findings in the booklet group, we recorded a statistical and clinically significant improvement in IBDQ-B score in both the gastroenterologist group 10·4 (10·3; 7·7–13·1) and the nurse group of 9·1 (8·84; 6·9–11·2), a pair-wise mean difference in change of gastroenterologist versus booklet of 5·47 (95% CI 1·14–9·81; p=0·01) and nurse versus booklet of 4·12 (0·04–8·19; p=0·04).

No statistical analysis between the three groups was planned for the second timepoint at 12 months as a result of the crossover from booklet to gastroenterologist group. However, to assess whether benefit seen in both the nurse and gastroenterologist groups from baseline to 6 months was maintained up to 12 months, we did pair-wise comparisons on IBDQ-bowel scores within the gastroenterologist and the nurse groups between the three timepoints. In addition to the improvement seen between baseline and 6 months, we also recorded an improvement in IBDQ-bowel score between baseline and 12 months in both the gastroenterologist group (Mean 10·97, SD 11·05; p<0·0001) and the nurses group (6·13, 11·65; p<0·0001). Finally, we recorded no difference in IBDQ-bowel scores in either the gastroenterologist or nurse group between months 6 and 12 (mean change 1·45 [p=0·2] in the gastroenterologist group and –2·27 [p=0·1] in the nurse group). This finding shows that improvements seen between baseline and 6 months in these two groups are maintained through 12 months.

The mean difference in IBDQ-B scores between the gastroenterologist and nurse groups at 6 months was 1·36, which was much lower than the score of 4 hypothesised to indicate that nurse-led care was not worse than gastroenterologist-led care. The one sided 95% CI was –1·48, highly suggestive that outcomes were not worse in the nurse group.

Four patients crossed over from the nurse group to the gastroenterologist group 15–32 weeks after randomisation. The reasons for crossover were: severe anal pain in two patients, which was unresolved despite following all steps suggested by the algorithm; one patient who had

other medical problems that made management of the gastrointestinal problems very complex; and one patient who had multiple symptoms which did not respond to algorithmic management.

The change in other, secondary endpoint gastrointestinal measures, in addition to quality of life and depression scores are shown in tables 4 and 5. The study was not powered to assess these formally, but there seemed to be improvement in the IBDQ and slight improvement in the St Mark's Incontinence score in the treatment groups. HAD anxiety seemed to improve at 6 months, but HAD depression seemed to worsen, which is possibly related to very large changes in scores from baseline in a small number of individuals at 6 months (see appendix for assessment of urinary and sexual function).

Mean improvement in IBDQ-B scores after 6 months in the booklet group was 4·9 (SD 13·5), which is not considered clinically significant. 30 (44%) of 68 patients in the booklet group requested gastroenterologist review after 6 months. We recorded no statistically significant difference in IBDQ-B or IBDQ at baseline (p=0·25) between patients who subsequently switched at 6 month and those who did not. However, at 6 months, compared with those who did not ask to see a gastroenterologist, patients who asked to see a gastroenterologist had significantly worse IBDQ-B score (53·9 [SD 14·3] *vs* 61·4 [9·9]; p=0·03) and IBDQ scores (168 [45·5] *vs* 192 [26·6]; p=0·02). Patients' IBDQ-B scores improved 6 months after they had switched to the gastroenterologist group by a mean of 3·7 (SD 14·2) and their overall IBDQ score improved by a mean of 12·1 (33·4), but these scores after 6 months of active intervention remained significantly worse than those who did not choose to switch groups and had by this point been followed up for 1 year (IBDQ-B 64·2 for patients who stayed in the booklet group *vs* 57·6 for patients who switched [p=0·02]; IBDQ 197 *vs* 180 [p=0·046]).

See Online for appendix

Regular audit by the steering group confirmed 100% compliance by nurse and gastroenterologist with the algorithm and high accuracy of data entry into the trial data base (<1% error rate). 17 (8%) patients were recruited with less than 6 months follow-up from the

	n	Booklet group	Gastroenterologist group	Nurse group
IBDQ-B subset <60 (ie, moderate to severe) at randomisation	145	43 (63%)	48 (69%)	54 (67%)
IBDQ-B subset ≥60 (ie, mild) at randomisation	73	25 (37%)	22 (31%)	26 (33%)
IBDQ-B score at randomisation	218	51·8 (12·9)	52·1 (10·8)	53·0 (10·4)
IBDQ-B score at 6 months	182	57·5 (12·9)	62·3 (8·4)	62·0 (10·2)
IBDQ-B score at 12 months	180	60·6 (10·4)	62·7 (7·6)	59·6 (12·5)

Data are n (%) or mean (SD). IBDQ-B=Inflammatory Bowel Disease Questionnaire – Bowel. A score of 10 means the worst possible bowel function and one of 70 means perfect bowel function.

Table 3: **Change in IBDQ-B score**

	n	Booklet group		Gastroenterologist group		Nurse group	
		Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)
IBDQ–B (best possible score=224, worst=36)							
At randomisation	218	..	167 (39·3)	..	171 (28·6)	..	169 (33·3)
At 6 months	182	..	180 (39·3)	..	192 (22·8)	..	189 (32·2)
At 12 months	180	..	188 (30·0)	..	194 (22·2)	..	184 (36·0)
St Mark's Incontinence score (0=perfect continence, 24=total incontinence)							
At randomisation	217	..	8 (0 to 22)	..	8 (0 to 20)	..	8 (0 to 22)
At 6 months	180	..	6·5 (0 to 22)	..	5 (0 to 20)	..	4·5 (0 to 18)
At 12 months	179	..	6 (0 to 20)	..	6 (0 to 18)	..	5 (0 to 21)
Change in rectal LENT SOMA (best possible score=0, worst=56)							
At randomisation	218	..	..	..	..	..	..
At 6 months	196	–0·04 (0·2)	–0·05 (–0·6 to 0·7)	–0·10 (0·17)	–0·05 (–0·6 to 0·3)	–0·12 (0·17)	–0·10(–0·8 to 0·25)
At 12 months	186	–0·05 (0·2)	–0·05 (–0·6 to 0·7)	–0·09 (0·19)	–0·05 (–0·5 to 0·6)	–0·08 (0·19)	–0·05 (–0·6 to 0·6)
Change in small intestine LENT SOMA (best possible score=0, worst=52)							
At randomisation	218	..	..	..	..	..	..
At 6 months	196	–0·04 (0·15)	–0·06 (–0·6 to 0·2)	–0·10 (0·12)	–0·12 (–0·6 to 0·2)	–0·09 (0·12)	–0·06 (–0·5 to 0·1)
At 12 months	186	–0·08 (0·15)	–0·06(–0·5 to 0·3)	–0·07 (0·13)	–0·06(–0·4 to 0·4)	–0·07 (0·12)	–0·06(–0·5 to 0·2)

Data are mean (SD) or median (range). IBDQ-B=Inflammatory Bowel Disease Questionnaire – Bowel. LENT= Late Effects of Normal Tissues. SOMA=Subjective-Objective Management Analytic.

Table 4: **Change in score of the gastrointestinal secondary endpoints**

	n	Booklet group			Gastroenterologist group			Nurse group		
		Mean change (SD)	Mean (SD)	Median (range)	Mean change (SD)	Mean (SD)	Median (range)	Mean change (SD)	Mean (SD)	Median (range)
Work and social adjustment scale (WASA; best possible score 40)										
At randomisation		..	..	..	..	..	..	..	..	..
At 6 months	178	−0·26 (7·59)	..	0 (−19 to 25)	−1·40 (6·43)	..	0 (−20 to 14)	−1·89 (6·44)	..	0 (−27 to 13)
At 12 months	179	−2·30 (7·27)	..	0 (−22 to 22)	−1·86 (6·71)	..	−1 (−12 to 23)	−0·67 (7·03)	..	0 (−20 to 21)
HAD anxiety*										
At randomisation	216	..	..	..	..	..	..	..	..	..
Scores <11	181	..	58 (85)	..	..	59 (86)	..	..	64 (81)	..
Scores ≥11	35	..	10 (15)	..	..	10 (14)	..	..	15 (19)	..
At 6 months	180	..	..	..	..	..	..	..	..	..
Scores <11	161	..	53 (93)	..	..	52 (91)	..	..	56 (85)	..
Scores ≥11	19	..	4 (7)	..	..	5 (9)	..	..	10 (15)	..
At 12 months	181	..	..	..	..	..	..	..	..	..
Scores <11	161	..	53 (88)	..	..	52 (90)	..	..	56 (89)	..
Scores ≥11	20	..	7 (12)	..	..	6 (10)	..	..	7 (11)	..
HAD depression*										
At randomisation	216	..	..	..	..	..	..	..	..	..
Scores <11	209	..	66 (97)	..	..	67 (97)	..	..	76 (96)	..
Scores ≥11	7	..	2 (3)	..	..	2 (3)	..	..	3 (4)	..
At 6 months	180	..	..	..	..	..	..	..	..	..
Scores <11	172	..	55 (97)	..	..	53 (93)	..	..	64 (97)	..
Scores ≥11	8	..	4 (7)	..	..	4 (7)	..	..	2 (3)	..
At 12 months	181	..	..	..	..	..	..	..	..	..
Scores <11	168	..	54 (90)	..	..	55 (95)	..	..	59 (94)	..
Scores ≥11	13	..	6 (10)	..	..	3 (5)	..	..	4 (6)	..
SF12 quality of life										
PCS change in score										
At 6 months	176	−0·26 (6·79)	..	−3 (−16 to 19)	3·30 (10·18)	..	1·4(−27 to 32)	−0·57 (6·63)	..	−0·3 (−0·2 to 0·2)
At 12 months	173	0·06 (7·55)	..	0·2 (−17 to 18)	3·41 (9·65)	..	3·3 (−29 to 26)	−0·83 (8·40)	..	0 (−23 to 14)
MCS change in score										
At 6 months	176	0·32 (8·01)	..	0·4 (−18 to 19)	−1·42 (9·44)	..	−1·4 (−28 to 20)	0·53 (8·06)	..	0 (−25 to 26)
At 12 months	173	1·12 (7·95)	..	1·7 (−20 to 22)	0·11 (11·5)	..	0·7 (−26 to 27)	−0·59 (8·89)	..	−0·6 (−0·3 to 18)

HAD=hospital anxiety and depression scale. MCS=mental component summary scales. PCS=physical component summary scales. *Possible scores range from 0 to 21 for each subscale, which is then divided into four ranges: mild cases (scores 8–10), moderate cases (scores 11–15), and severe cases (scores of 16 or higher).

Table 5: **Changes in quality-of-life secondary endpoints**

end of radiotherapy because the start date of radiotherapy was erroneously used to calculate the length of time of follow-up. Two patients recruited 4·4 months and 4·5 months after the end of radiotherapy were withdrawn from the analysis but the other 15 patients (recruited at 5 or more months) were included. Five of these patients were randomly allocated to the booklet, six to the gastroenterologist group, and four to the nurse group.

Although the covariates seem balanced across groups, there were fewer women than men in the study. And although median age seemed balanced across groups, the ranges of age were not. Therefore, we did an analysis of variance (ANOVA) parametric analysis model using treatment groups, age, sex, and the interaction between age and sex. This analysis showed a significant difference in outcome between the three groups overall (p=0·007) as well as with age (p=0·013). However, age and interaction between age and sex did not affect outcome (p=0·184 for age and p=0·291 for age and sex).

Because there were more men with prostate cancer than men or women with any other tumour type, we did an additional subgroup analysis in the urology group by itself to exclude potential biasing of the results. This analysis showed almost identical outcomes to those seen when patients with tumours at all sites were analysed: IBDQ-Bowel mean change scores at 6 months were significantly different between booklet versus consultant (p=0·012), booklet versus nurse (p=0·040) and booklet versus combined intervention groups (p=0·006).

Discussion

Our findings show that a structured, algorithm-driven approach to management can give clinical improvement in bowel function, that a nurse can deliver this care effectively using our trial algorithm in most patients, and that this benefit is sustained over time.

UK data suggest that only one in five patients who develop gastrointestinal problems affecting quality of life after pelvic radiotherapy are referred to a gastrointestinal specialist. Patients report that many of those consultations are unsatisfactory because few gastroenterologists are confident about how to manage their symptoms.[9] There has been no improvement in gastroenterologists' expertise in this field in the past decade.[33,34]

Very large numbers of patients are affected by pelvic radiation disease, so the fact that this is the first prospective randomised study that has attempted to show that overall gastrointestinal function can be improved is surprising. However, it is not surprising that intervention is useful. Many of the changes in gastrointestinal physiology induced by radiotherapy have been defined in clinical series published over many years.[35] The only unusual feature of radiation-induced gastrointestinal injury that might differ from other diseases seen routinely in gastroenterology clinics is that patients often have more than one serious gastrointestinal physiological abnormality due to the extent of intestinal radiation exposure.[36] Tests to define which physiological abnormalities are present are routinely used in gastroenterological practice. When specific abnormalities are diagnosed, for example malabsorption of carbohydrate or bile acids, or small bowel bacterial overgrowth, there are evidence-based treatments which can be used.

In inflammatory bowel disease, a disorder with some similarities to pelvic radiation disease for which specialist nurses often manage patients, findings from a Cochrane review showed little evidence of any effect of nurse-led care due to an absence of high quality trials.[37] We know of no previous controlled studies of the effectiveness of nurse management of radiation injury. However, conceptually, the development and testing of algorithms remains appealing because it could improve the management of complex gastrointestinal symptomatology and might be effective in more than one context. Nurse-managed clinics are a cost-effective alternative for medical management and education of patients and have been shown to provide high quality health care for a range of disorders, including cancers.[38,39] Nurse intervention improves faecal incontinence.[40–42] Nurse-delivered care has similar outcomes to that of doctor-led care, but with higher patient satisfaction and is popular with patients and their support groups[43,44] despite involving more diagnostic tests than doctor-led care.[45]

The fact that patients with problematic bowel function after radiotherapy clearly benefit from intervention increases the rationale for actively seeking out such patients. At present, most patients have to be very determined before they achieve referral for specialist assessment as it is widely believed that they suffer from an untreatable condition (5). In the UK, the national network of nurses supporting patients with cancer could potentially be trained to detect, assess and manage gastrointestinal symptoms with people after pelvic radiotherapy.

This study was designed to assess the effect of treatment of gastrointestinal symptoms, but our findings also suggest that the adverse effects of radiation treatment are not restricted to the gastrointestinal tract—patients reported a wide range of symptoms affecting all the pelvic organs. The trial was not powered to detect the effect of intervention for gastointestinal symptoms on quality of life, but there does not seem to be obvious change in any group. This finding might be because although intervention improved patients' gastrointestinal symptoms, many had other unresolved symptoms affecting their urinary, sexual, or lymphatic systems.

There is no ideal score to measure improvement in bowel function. However, the IBDQ-Bowel subset score is a direct measure of bowel symptoms. In previous studies,[46] a change of score of more than 6 points has been shown to be clinically significant. Although a change of score of less than 6 points might be clinically relevant to individuals in specific circumstances, an improvement in score of less than 6 points (as occurred in the booklet group) is not thought to be clinically significant.

Although a third of patients included in this study had symptoms classified as mild (IBDQ-B score >60), such symptoms can have a substantial effect. For example, a patient who has urgency of defecation, and as a result

Panel: Research in context

Systematic review

Before starting the trial and on completion of this study, we searched PubMed, ISI Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), Medline (1966–2013), Embase (1980–2013), CINAHL (1982–2013), and The British Nursing Index (1985–2013) for randomised controlled clinical trials of gastroenterological or nurse-led management of radiation-induced gastrointestinal toxic effects in patients who had undergone radical pelvic radiotherapy. We used search terms that included radiation proctitis, enteritis, proctopathy, enteropathy, pelvic radiation disease, late effects, and consequences of treatment—we found no previous studies. Cohort studies of variable quality and size, and involving various patient groups over many years have identified multiple physiological abnormalities that can develop in the gastrointestinal tract after therapeutic irradiation for a pelvic tumour.[12] A logical peer reviewed algorithmic approach to managing these physiological abnormalities systematically was produced and has been tested in two small pilot studies to apparent benefit.[13,19]

Interpretation

Our controlled, randomised study robustly shows that managing this large patient group with a systematic approach is effective and that management can be delivered in most patients effectively by a specially trained nurse. The study result mandates a radical shift in the attitude that the only important aspect of aftercare for patients after pelvic radiotherapy is surveillance for tumour recurrence and suggests that every oncology unit needs to develop a specialist pathway to manage the common complications of pelvic cancer irradiation.

hardly leaves their house, might be rarely incontinent and so have little opportunity to improve this symptom score but their quality of life would be detrimentally affected. Urgency of defecation is considered by patients to be one of the most distressing gastrointestinal symptoms,[15] although most radiotherapy toxicity scoring systems do not ask about it. We recorded only small improvements in overall St Marks Faecal incontinence scores, a simple but very effective measure of urgency and incontinence, but even small improvements in those symptoms can afford a patient much greater feelings of control.

Half the patients in the booklet group improved and did not want further intervention, but patients who subsequently crossed over to the gastroenterologist group did not seem to achieve the improvement that patients achieved who were initially randomised to active treatment. Therefore, the booklet could be offered to all patients with new symptoms at the earliest stage possible and active intervention be offered to those who do not respond rapidly to help prevent symptoms becoming established. Such an approach could save money by avoiding consultations and tests.

A full cost-effectiveness analysis was embedded within the trial. The results will be reported separately. However, the algorithm comprised simple routine tests and was delivered at a small cost. Therefore, our findings suggest that a change is needed in the attitude that the only important aspect of care for patients after pelvic radiotherapy is surveillance for tumour recurrence. Although robust oncological follow-up should continue in these patients, our trial suggests that many patients are unnecessarily tolerating chronic symptoms and that every oncology unit needs to develop a specialist pathway not only to manage the gastrointestinal complications of pelvic cancer irradiation but also a holistic assessment approach to encompass other non-gastrointestinal symptoms. Such action will help acknowledge the wider psychosocial and emotional context of chronic toxicity and is likely to promote development of useful treatments for other affected pelvic organs.

Contributors

All authors contributed to the study design and trial protocol. HJNA, BEB, CN, and JOL developed the algorithm. HJNA, AL, HG KP, and KH developed the economic and statistical plan. All authors contributed to the organisation and conduct of the study. Patient recruitment and acquisition of data was done by by HJNA, BB, and AL. All authors contributed to the analysis and interpretation of study data. HJNA prepared the draft paper and all authors subsequently reviewed the output and made revisions.

Conflicts of interest

We declare that we have no conflicts of interest.

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