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Nutritional strategies to prevent gastrointestinal toxicity during pelvic radiotherapy

Linda J. Wedlake

Royal Marsden Clinical Trials Unit, The Royal Marsden NHS Foundation Trust, Sutton, Surrey, UK

Radiotherapy-induced damage to non-cancerous gastrointestinal mucosa has effects on secretory and absorptive functions and can interfere with normal gastrointestinal physiology. Nutrient absorption and digestion may be compromised. Dietary manipulation is an attractive option with sound rationale for intervention. The aim of this review was to synthesise published evidence for the use of elemental formulae, low or modified fat diets, fibre, lactose restriction and probiotics, prebiotics and synbiotics to protect the bowel from gastrointestinal side effects during long-course, radical pelvic radiotherapy. Thirty original studies (recruiting *n* 3197 patients) were identified comprising twenty-four randomised controlled trials, four cohort studies and two comparator trials. Endpoints varied and included symptom scales (Inflammatory Bowel Disease Questionnaire, Common Technology Criteria for Adverse Events, Radiation Therapy Oncology Group) and Bristol Stool Scale. Dietary and supplement interventions were employed with many studies using a combination of interventions. Evidence from RCT was weak for elemental, low or modified fat and low-lactose interventions and modestly positive for the manipulation of fibre during radiotherapy. Evidence for probiotics as prophylactic interventional agents was more promising with a number of trials reporting positive results but strength and strains of interventions vary, as do methodologies and endpoints making it difficult to arrive at firm conclusions with several studies lacking statistical power. This consolidated review concludes that there is insufficient high-grade evidence to recommend nutritional intervention during pelvic radiotherapy. Total replacement of diet with elemental formula could be effective in severe toxicity but this is unproven. Probiotics offer promise but cannot be introduced into clinical practice without rigorous safety analysis, not least in immunocompromised patients.

Pelvic radiotherapy: Toxicity: Gastrointestinal: Nutrition: Dietary intervention

Therapeutic pelvic radiotherapy

The delivery of therapeutic, high-voltage, ionising radiation (radiotherapy) with the explicit intention of destroying cancerous cells remains a critical component of cancer treatment. Over 50 % of patients will receive radiotherapy at some time during the management of their malignant disease[1] either alone or in combination with surgery and/or chemotherapy. The most common treatment modality is external beam radiotherapy which is delivered in the form of very high-energy, collimated and flattened X-ray beams of 4–25 Mega electron volts generated by a linear accelerator or Linac. The term pelvic cancer refers to cancers that arise within the pelvis (i.e. volume extending from lumbar vertebra L4 to the anal verge[2]) and includes tumours of a gynaecological, urological or lower gastrointestinal origin. In the UK in 2011 of all new cancer diagnoses, 35 % (116 294) were of pelvic origin[3].

Designed to be skin-sparing, radiotherapy beams penetrate the human body to predetermined depths to

Abbreviations: CFU, colony-forming units; IDBQ-B, inflammatory bowel disease questionnaire-bowel; LCT, long-chain TAG; MCT, medium chain TAG; RCT, randomised controlled trials.

Corresponding author: Linda Wedlake, email Linda.Wedlake@rmh.nhs.uk

destroy cancerous cells through the process of ionisation (i.e. the displacement of an electron from its orbital path and the creation of an unstable or ionised atom and free electron) with ensuing particle chain reactions and free radical-mediated damage. The nuclear DNA of cancer cells is the primary target of this planned radiobiological destruction. The effects may be immediate cellular ablation or, often quantitatively more significant, latent but permanent damage which is expressed when the tumour cells attempt to divide and replicate.

Total prescribed radiotherapy dose is defined in Gray (Gy) the SI unit of absorbed radiation dose. The prescribed radiation dose, which for long-course treatments is typically 45–54 Gy, is divided into a series of equal daily fractions. Thus, a prescription dose of 45 Gy delivered at a rate of 1·8 Gy/fraction would require the patient to attend for twenty-five treatments over an elapsed time of at least 5 weeks, assuming a Monday–Friday treatment schedule.

Fractionation is intended to exploit the differential in the cytotoxic effect of ionising radiation on cancerous *v.* normal tissue, reparative processes being generally greater in normal tissues through which the radiation beams inevitably pass to reach their target. For any given tumour, the greater the reparative powers of normal cells compared with cancerous cells, the wider the therapeutic window and thus the increased certainty of tumour control with minimised damage to normal cells.

Estimating the number of patients treated with curative, long-course (radical) pelvic radiotherapy in the UK is complicated by the fragmentation of UK cancer registries and the lack of uniformity in data reported. The most recent quantitatively based estimate reported that 12 000 patients received long-course pelvic radiotherapy annually[4]. However, this figure, derived in 2003 is likely to have risen in the past 15 years. Taking the USA and Western Europe combined, it is estimated that at least 300 000 patients annually receive long-course, fractionated, curative radiotherapy for pelvic cancers.

Treatment-induced toxicity

The term toxicity refers to unwanted radiation-induced damage or injury (sometimes referred to as side effects) to normal tissues as distinct from planned destruction of malignant cells. Despite major advances in the planning and delivery of radiotherapy and the introduction of new radiotherapy techniques such as image-guided radiotherapy, intensity-modulated radiotherapy and stereotactic radiotherapy the tolerance of normal tissues to irradiation remains dose-limiting.

For pelvic tumours, treatment-induced gastrointestinal toxicity is an unwanted side effect of treatment causing significant acute and chronic morbidity of varying severity. Portions of the bowel that lie within the radiotherapy field include the distal portion of the small bowel, the terminal ileum, the caecum, the large bowel including the ascending, mid-transverse, sigmoid colon and rectum. In wide pelvic fields, which may encompass pelvic lymph nodes, it is not uncommon for loops of the small bowel or transverse colon to dip down into the field thus also receiving radiation dose. Treatment margins which allow for systematic and random errors in treatment delivery add to the overall treatment volume and thus increase risk of normal tissue toxicity.

During a course of fractionated pelvic radiotherapy up to 90 % of patients experience gastrointestinal symptoms of varying severity due to the close proximity of the bowel to the pelvic organs[4]. Symptoms experienced during treatment include a change in bowel habit (94 %), loose stool (80 %), bowel frequency (74 %), urgency (39 %) and fecal incontinence (37 %). Once radiotherapy ceases, bowel-related symptoms continue to emerge with 50 % of patients describing them as having a detrimental effect on quality of life[5–11]. As the number of long-term survivors of pelvic cancer continues to grow, estimated to be in excess of three million in the USA in 2013, strategies to limit its damaging side effects are acknowledged as becoming increasingly important[12].

Radiation-induced toxicity has historically been divided into acute and late reactions or effects[13]. Acute reactions are defined as those occurring during treatment or within 3–6 months of treatment and may lead to symptoms. Late reactions may occur months or years after treatment ranging in severity from mild and treatable to irreversible, severe or fatal. Serious and life-threatening changes including transfusion-dependent bleeding, fistula formation and bowel obstruction have been reported in 4–10 % of patients 5–10 years after treatment[14,15] and in 15–20 % of patients 20 years or more after pelvic radiotherapy[16].

Mechanisms of normal tissue damage

Radiation-induced damage to normal tissues has been compared with a complex wound and is essentially an inflammatory process[17]. Studies investigating changes in the morphology of the rectal wall which have been conducted in patients during the acute phase of treatment[18,19] have revealed that symptoms tend to start during the second week of treatment (when histological damage is at a maximum) and peak towards the end of treatment (weeks 4–5) when histological changes are stabilising or even improving. Early lesions resulting from inflammatory insult may resolve following treatment but changes consistent with chronic ischaemia and fibrosis can emerge months or years later resulting in functional impairment to normal gastrointestinal physiology and a spectrum of clinical outcomes now defined as pelvic radiation disease[20].

Radiotherapy-induced gastrointestinal toxicity

Mucosal biopsies from superficial layers of irradiated rectal wall have revealed changes which include atrophy of surface epithelium, acute inflammation of the crypts, inflammatory cell infiltration of surface epithelium, accumulation of eosinophilic granulocytes[18], flattening of columnar cells, loss of goblet cells, oedema[18] and excessive collagen deposition[19]. Nutritionally related effects of these changes include: disaccharidase malabsorption (notably lactose, fructose[21–23] and possibly sucrose), bile acid

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malabsorption[24,25], fat malabsorption, dysmotility[26,27] and small bowel intestinal bacterial overgrowth[23]. Whilst these effects are predicated by specific aberrations in gastrointestinal functionality they commonly have the same clinical endpoints, bowel disturbance, malabsorption and abnormal stool.

Potential role of dietary modulation

It is now well established that a severe acute reaction during radiotherapy increases the risk of severe late or chronic effects[28,29] and further that cumulative but sustained mild or moderate toxicity may be more damaging than a single severe peak of symptoms[30]. Therefore, strategies that offer moderate but prolonged protection throughout radiotherapy by limiting the acute inflammatory processes affording some protection against self-perpetuating fibrotic processes may be effective. In this context, there is a sound physiological rationale for a number of specific nutritional interventions, the evidence for which is explored later.

This review paper examines the evidence for the efficacy of nutritional manipulation during radical pelvic radiotherapy. Randomised controlled trials (RCT), controlled trials with comparator groups and cohort studies recruiting adult patients, receiving radical daily radiotherapy for pelvic malignancies, employing (oral) nutritional or dietary interventions and reporting outcomes related to gastrointestinal symptoms or treatment-induced toxicity have been included. Studies investigating more than one nutritional intervention are described with respect to the primary intervention. Four previous reviews on this topic have been published, two systematic reviews[31,32] and two Cochrane reviews[33,34]. The current paper summarises results of these previous reviews for most commonly trialled nutritional interventions including; elemental diet, low or modified fat diet, lactose-restricted, fibre and probiotic/prebiotic/synbiotic combinations. Results are presented for each nutritional intervention under the headings: rationale, evidence and conclusion. The data were presented at the Winter Meeting of the Nutrition Society, London, 2017.

Methods

This paper is compiled from data published in two non-Cochrane[31,32] and two Cochrane reviews[33,34]. Readers are referred to these publications for a detailed description of methods employed.

Results

Elemental formulae

Rationale. Elemental nutritional formulae provide essential macronutrients in readily digestible (liquid) form with protein supplied as amino acids or peptides, fats primarily as medium chain TAG (MCT) and carbohydrates largely as maltodextrins. In appropriate quantities, these formulae contain all essential macro and micronutrients and can be used as a sole source of nutrition for prolonged periods. The rationale for their use during radiotherapy is 2-fold: first, the provision of nutrients that can be readily absorbed by the gastrointestinal mucosa and secondly their potential to reduce pancreatic and biliary secretions which may aggravate pre-existing mucosal inflammation. Delivery of elemental formula to the mid-distal and distal jejunum can suppress pancreatic secretions[35,36] whilst delivery of elemental formula to the proximal duodenum suppresses maximal mean post-prandial pancreatic secretions by up to 50 %, compared to polymeric formula, in healthy human volunteers[37].

Evidence. Six studies, four RCT[38–41] and two comparator trials[42,43] have recruited 836 patients. One study[41] is an analysis of a sub-group of patients recruited to a larger RCT[38]. All studies were preventative in aim with elemental formula providing between 33 and 100 % of daily energy needs. Two studies used elemental formula as the sole nutritional intervention[40,43] the remaining studies advised patients to additionally follow a low-fibre diet[38,41] a low-fibre, lactose-restricted, low-fat diet[42] or a natural diet (not defined)[39]. All studies (except one[43]) used an interventional period of between 3 and 6 weeks coincident with radiotherapy treatment. The largest study (n 677) reported a significant reduction in the proportion of patients experiencing radiotherapy oncology group toxicity grades 1 and 2 in those patients in the elemental group *v.* those consuming a standard diet but did not report a significance value[39]. However, a significant decrease ($P < 0{\cdot}05$) was reported in the number of patients whose treatment was interrupted due to toxicity in the elemental group *v.* the standard diet group. In three further studies[38,40,41], no significant differences between elemental and non-interventional groups were reported in mean stool frequency[38], time to onset of diarrhoea[38], change in Inflammatory Bowel Disease Questionnaire-bowel score (IBDQ-B)[40], change in inflammatory marker fecal calprotectin[40] or change in markers of nutritional status[41]. Compliance with elemental prescription was a concern. In one study[38], 41 % of patients were unable to tolerate the elemental formula for the prescribed period and in another study, mean dose of formula taken was just 21 % of daily energy requirement compared with the prescribed 33 %[40].

Two further non-randomised studies have been reported: a phase II investigation of seventeen patients with gynaecological cancer receiving a 4/5-week course of treatment[42] and a study which commenced as an RCT in patients receiving pre-surgical, short-course radiotherapy for invasive bladder cancer[43]. In the latter study, the interventional period was for just 5 d with elemental formula providing 100 % of energy intake[43]. The phase II study (which additionally asked patients to reduce fibre, lactose and fat) reported a significant reduction ($P < 0{\cdot}001$) in the proportion of compliant patients experiencing radiotherapy oncology group grade 2/3 diarrhoea together with a reduced need for anti-diarrhoeal medication[42]. Compliance was reportedly high in the elemental group with 76·5 % of patients taking the prescribed formula for >80 % of the time. In the short-course study, randomisation to the

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conventional feeding group (normal hospital diet or parenteral nutrition) was halted after a benefit was identified in just four patients receiving elemental feeding[43]. The authors reported a significant reduction ($P < 0{\cdot}001$) in the incidence of severe post-operative diarrhoea in elementally fed patients when compared with a retrospective group receiving conventional feeding.

Conclusion. Evidence for the efficacy of elemental formula from RCT is weak. Whilst the sole study[39] which did report improved outcomes was by far the largest, it is published in abstract only. Three further studies failed to provide evidence of efficacy although these suffered from poor compliance and thus it is unclear whether the intervention itself was ineffective or the lack of endpoints in non-compliant patients resulted in underpowering[38,40,41]. One non-RCT in which diet was completely replaced with the elemental formula provided evidence of efficacy in pre-surgical patients in a short-term setting albeit using retrospective controls[43]. Whether 100 % replacement of normal diet with elemental formula could be achieved in patients during long-course radiotherapy is debatable.

Low or modified fat diets

Rationale. Fat intake in health comprises approximately one-third of total energy requirements (approximately 95 g fat/d (males), 70 g fat/d (women)[44]. Dietary fats comprise long-chain TAG (LCT) with (three) fatty acids, mostly twelve to eighteen carbon atoms in length. In contrast, MCT comprise fatty acids of eight to fourteen carbon atoms in length which are absorbed directly into the portal blood. They occur in only a few foods (e.g. coconut) but may be prescribed in supplement form under medical or dietetic supervision. The rationale for the use of low or modified fat (MCT-predominant) diets during radiotherapy is 4-fold. Damage to the gastrointestinal brush border[45] may reduce its ability to absorb LCT, high-fat (LCT-based) diets may be pro-inflammatory[46], reduced production of bile acids may occur [25,47] and MCT do not stimulate exocrine pancreatic secretions (specifically amylase and lipase)[48] sparing gastrointestinal mucosa from the proteolytic effects of these enzymes.

Evidence. Four RCT recruiting 316 patients[21,25,49,50] have examined the efficacy of low or modified fat diets. All studies were preventative in aim. Dietary interventions were used in all four studies with a low LCT fat arm consuming 20 g/d[41] and 40 g/d[21,25,50]. Interventional strategies differed, two studies[49,50] used MCT-based supplements to compensate for reduced total energy intake, lactose was additionally restricted in one study[21] and in another[25] all patients were instructed to follow a low-fat diet but were randomised at 2 weeks to receive the bile acid binder cholestyramine (4 g twice daily) or placebo. Two studies[21,25] reported benefits associated with a low-fat intervention. In one, significant differences between patients consuming a low-fat, low-lactose diet *v.* patients on a regular (hospital) diet were reported including a halving of the incidence of new-onset diarrhoea, a 50 % reduction ($P < 0{\cdot}01$) in the mean number of anti-diarrhoeal tablets used and a significant reduction ($P < 0{\cdot}01$) in the number of loose, watery stools per week[21]. In the other, diarrhoea control was significantly better ($P < 0{\cdot}05$) in the cholestyramine arm although >50 % patients in this group reported side effects, including nausea and abdominal cramps[25].

In the remaining two studies, one reported reduced bowel frequency in the low-fat MCT-supplemented group *v.* the low-fat group although results were NS and the difference in frequency modest (mean 1·6 (SD 0·9) *v.* 2·0 (SD 1·0) movements daily)[49]. The other study used a three-arm design to compare a normal fat diet *v.* low fat *v.* low fat + MCT supplement (50:50 ratio of LCT:MCT) and reported no significant difference in the fall in IBDQ-B scores or change in secondary nutritional endpoints between groups. Poor compliance in the normal fat group[50] resulted in the majority of patients consuming a diet with low LCT content. The authors commented that the fall in IBDQ-B score for the cohort (*n* 107) compared favourably with a mean pooled fall in score of −9 points from previous studies in similar cohorts (*n* 409) suggesting a positive impact of dietary intervention (irrespective of study arm) and/or a benefit of reduced fat intake across all groups[4,23,30,40].

Conclusion. Evidence for the efficacy of low LCT fat interventions is limited. Whilst two high-quality RCT provided evidence of efficacy, neither manipulated fat as the sole intervention making it difficult to determine which intervention was responsible for efficacy[21,25]. Although a third RCT[49] reported a modest benefit of low fat it is published in abstract only. The final adequately powered high-quality study found no significant difference in outcomes between groups although inadequate differential in fat intake between groups precluded robust conclusions[50].

Lactose restriction

Rationale. Lactose is a disaccharide of glucose and galactose found in milk and milk products. Typical quantities are 13·5 g/one-half pint (284 ml) milk (full cream or skimmed) with similar amounts in other dairy products such as yoghurt and ice cream. Lactose must be cleaved to its monomeric units before absorption by enzyme lactase present in the brush border. Unabsorbed lactose contributes to an osmotic load in the large intestine causing watery diarrhoea. In many races, a genetically programmed fall in lactase occurs after weaning resulting in intolerance to milk products. In white Caucasian populations (despite a mistaken tendency to attribute various abdominal symptoms to lactose intolerance[51]) endogenous lactase does not diminish with adulthood and genetically based lactase deficiency occurs in about 5–19 % of adults. Lactase deficiency may arise secondary to radiation-induced damage of the intestinal mucosa and depletion of brush border enzymes. Although the incidence of new-onset lactose intolerance during radiotherapy has not been definitively quantified, one small study[23] in a cohort of twenty-six patients has suggested that it may be about 15 %.

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Evidence. Three studies recruiting 118 patients have examined the incidence of lactose malabsorption[22,52] and the efficacy of a lactose-restricted (or modified) diet during treatment[53]. Two prospective case series[22,52] in white Caucasian cohorts have demonstrated new-onset lactose intolerance during pelvic radiotherapy. In the first of these studies, 50 % of (*n* 24) patients exhibited significantly reduced lactose absorption as assessed by ^{14}C lactose breath test[22] and a significant correlation ($P < 0{\cdot}05$) was reported between the breath test results at 5 weeks and increased stool frequency suggesting that patients with the most marked lactose malabsorption also had the most severe diarrhoea. A later study by the same group investigated the impact of volume of small bowel irradiated on lactose malabsorption[52] and found a clear separation in absorption rates in patients with large bowel volumes within the radiotherapy field compared with those with smaller volumes but no correlation between the change in breath test and stool frequency in either group.

Only one RCT has examined the efficacy of lactose restricted diets during pelvic radiotherapy[53]. In a three-arm study in which sixty-four mixed pelvic site patients were randomised to follow diets (supplemented with 480 ml milk) *v.* (lactose restriction (amounts not reported)) *v.* (supplemented with 480 ml milk + lactase enzyme) no benefit was found in any arm on multivariate analysis in reduced stool frequency or number of diarrhoea tablets used. The authors suggested that delayed gastric emptying following 5 weeks of radiotherapy may have confounded breath test results in the earlier studies[22,52] and/or that sites of maximal lactose absorption (mid-jejunum and upper ileum) escaped irradiation and/or that other factors (e.g. bile acid malabsorption) overwhelmed any benefit of the lactose restriction.

Conclusions. Whilst it is acknowledged that true lactose malabsorption is less prevalent than commonly supposed[51], limited evidence suggests that patients can become lactose intolerant during pelvic radiotherapy, but there is no evidence that restricting its consumption (or providing it in pre-hydrolysed form) is helpful. The sole RCT found no difference between groups in relevant gastrointestinal endpoints[53]. Whilst this study used an elegant design the published paper lacked data on study powering and given the 17 % drop out, the possibility of a type II error cannot be ruled out.

Dietary fibre

Rationale. The definition of fibre has been debated for years and measurement techniques vary. In 2008, a Codex (Codex Alimentarius Commission) Committee on Nutrition and Foods for Special Dietary Uses agreed on a definition of dietary fibre as carbohydrate polymers with ten or more monomeric units which are not hydrolysed by endogenous enzymes in the small intestine of human beings[54]. This definition encompasses naturally occurring, edible, plant-based polymers found in fruit, vegetables, seeds, nuts and cereals (i.e. those items promoted in the UK as components of 'healthy eating') and also extracted or synthetic carbohydrate polymers with proven physiological effects. Naturally occurring dietary fibre comprises both soluble and insoluble fractions with distinct properties. Both fractions occur naturally in most foods but one or the other normally predominates in extracted or synthetic supplements. Insoluble fibre is less easily fermentable than soluble fibre and provides stool bulk promoting healthy bowel physiology and motility. Soluble fibre (e.g. psyllium also called ispaghula or plantago ovate) provides a fermentable substrate for bowel microbiota, producing SCFA of which butyrate has received much attention due to its trophic, immune-modulatory and anti-inflammatory actions[55,56].

Evidence. Eight studies[57–65] recruiting 639 patients, comprising six RCT[57,59,61–65] (including one cross-over trial[57]) and two cohort studies[58,60] have explored the benefit of manipulating dietary and/or supplemental fibre during pelvic irradiation. Of the interventional RCT, two manipulated dietary fibre alone[60,65], three used a fibre supplement[59,63,64] (two of which included additional dietary restrictions[59,64]) and a further study with long-term follow-up manipulated dietary fibre in combination with a low-lactose restriction[61,62]. Seven studies[58–65] explored the role of fibre in preventing gastrointestinal toxicity (i.e. as a prophylactic agent) whilst one[57] explored the therapeutic efficacy of the psyllium *v.* codeine phosphate for the control of radiation-induced diarrhoea.

In the sole therapeutic RCT[57], patients receiving pelvic radiotherapy for gynaecological cancer were instructed to follow a low-fibre diet. A cross-over design was used to compare the efficacy of psyllium with codeine phosphate on presentation of treatment-induced diarrhoea[57]. The study was prematurely terminated after recruitment of ten patients due to lack of efficacy of psyllium, with all patients crossed-over to codeine phosphate. In the two-cohort studies[58,60], one reported favourable effects of a low residue diet[58] whilst the other, benefits or increased fibre consumption[60]. In the early large cohort study (*n* 156) in prostate cancer patients who were instructed to follow dietary restrictions (low residue, restricted caffeine, alcohol and spicy foods) throughout radiotherapy, improved genitourinary and gastrointestinal symptoms were reported in compliant *v.* non-compliant patients[58]. All non-compliant patients experienced side effects but grade 1 toxicity, which occurred in 41 % of these patients, was easily managed by reinforcement of dietary advice. In the smaller prospective cohort study[60] (*n* 22), prostate cancer patients were given individual advice to increase dietary fibre (and fluid) with the aim of stabilising rectal dimensions to prevent prostate deformation during treatment. Improved IBDQ-B scores were reported in those who met their fibre prescription *v.* those who did not although the study was not powered for this endpoint.

Of the three RCT which explored the efficacy of a fibre supplement[59,63,64], one reported reduced incidence ($P = 0{\cdot}049$) and severity ($P = 0{\cdot}030$) of diarrhoea (using a non-validated scale) in patients following a low-fibre, low-stimulant (caffeine and alcohol), low-fat diet plus a psyllium supplement *v.* those following the diet alone[59]. This study also reported a reduced need for anti-diarrhoeal

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medication in the diet plus psyllium group although the difference between groups was NS. A small placebo-controlled, double-blind, exploratory RCT[63] examined the efficacy of 3 g hydrolysed rice bran to prevent gastrointestinal toxicity in twenty patients receiving radiotherapy for cervical cancer. Frequency and severity of diarrhoea and use of anti-diarrhoeal medication was not significantly different between groups although the authors reported a reduced mean diarrhoeal assessment score in the hydrolysed rice bran group at 3 weeks compared with the control group. The study was not statistically powered and six patients were excluded from the final analysis due to failure to comply with an interventional prescription. Finally, the efficacy of an inulin + fructo-oligosaccharide prebiotic (6 g twice daily) to prevent acute radiation enteritis was examined in forty-six post-surgical gynaecology patients[64]. Patients in both the prebiotic group and placebo groups were additionally instructed to follow a low-fat, low-fibre and low-lactose diet for 1 week prior to radiotherapy, during treatment and for 3 weeks following treatment. A sample size of *n* 54 (twenty-seven per group) was required to detect a 10 % difference in the incidence of grade 2 diarrhoea (Common Technology Criteria for Adverse Events (CTCAE)). Of the thirty-eight patients with evaluable data, no difference between groups was observed in stool frequency although the number of days with loose stool (Bristol Stool Chart Type 7) was less in the prebiotic group ($P = 0{\cdot}008$). No differences were observed in time to onset of diarrhoea or use of anti-diarrhoeal medication.

The two most recent and larger RCT both used non-blinded dietary interventions. The first of these studies explored the efficacy of a low insoluble fibre + low lactose diet *v.* standard of care diet in 130 prostate cancer patients[61,62]. The intervention commenced 1 week prior to the start of radiotherapy and continued during radiotherapy with post-treatment follow-ups at 7, 12, 18 and 24 months[61,62]. A FFQ was designed to guide patients' food choices and monitor adherence to dietary instructions. A significant interaction effect ($P < 0{\cdot}001$) was noted between randomisation and time in FFQ scores, indicating compliance with intervention in both groups. Radiotherapy-induced toxicity was assessed using the prostate-specific QLQ-PR25 and European Organisation for Research and treatment of Cancer QLQ-C30 together with a non-validated study-specific Gastrointestinal Side Effects Questionnaire which assessed 'bother' associated with diarrhoea, blood in stool, mucous discharge, intestinal cramps, intestinal pain, intestinal gas and flatulence. Despite a trend towards reduced incidence of symptoms (using selected variables taken from the QLQ-PR25) no significant differences between groups in any gastrointestinal toxicity or quality of life measures were found in the short-term results at 2 months[61]. Incidence of self-reported diarrhoea at 8 weeks (end of radiotherapy) was slightly less in the interventional group 30 % (fourteen of fifty-one patients) *v.* the standard care arm 33 % (nineteen of sixty patients) but NS. At 24 months, evaluable data were obtained for 102 patients (attrition rate of 22 %). The authors again reported no obvious effect of the interventional diet on gastrointestinal symptoms or health-related quality of life at any time-points post-treatment[62]. The authors noted that the study may have been underpowered due to the lack of observable events (33–50 % of patients reported no symptoms during radiotherapy)[61] and an assumption at study powering with respect to bowel symptom scores that turned out to be incorrect.

The second, most recent RCT randomised 166 patients with mixed pelvic malignancies to low-fibre (≤10 g/d NSP), habitual (control) or high-fibre (≥18 g/d) diets during radiotherapy[65]. Patients received individualised counselling at the start of radiotherapy to achieve their dietary targets with study-specific instructional booklets for guidance. The primary endpoint was the difference between groups in the change in the IBDQ-B score between start and nadir (worst) score during treatment. Other measures included macronutrient intake, stool diaries and fecal SCFA. Fibre intakes were significantly different between groups ($P < 0{\cdot}001$) both at the start and end of radiotherapy indicating adherence to interventional prescription. The difference between groups in the change in IBDQ-B score between start and end of radiotherapy was smaller in the high-fibre group compared with the habitual fibre group ($P = 0{\cdot}011$) thus indicating a benefit of high-fibre consumption. This difference between groups was maintained at 1-year post-radiotherapy ($P = 0{\cdot}004$) prompting the authors to conclude that restrictive, non-evidence based advice to reduce fibre intake during radiotherapy should be abandoned. However, despite this important observation, it was noted that a dose–response relationship was not observed with the low-fibre group (who consumed the least amount of fibre) faring better than the habitual fibre group. No significant differences were observed in stool frequency, form or SCFA concentrations although the study was not powered for these endpoints. Significant reductions in energy, protein and fat intake occurred in the low and habitual fibre groups only. In addition, it was noted that high-fibre intake had no adverse effect on satiety, total energy intake or stool form.

Conclusions. There is moderately convincing evidence that increasing, rather than reducing fibre intake during pelvic radiotherapy has beneficial effects. Two studies using dietary manipulation[60,65] and three[59,63,64] using supplements reported improved bowel symptom scores[60,65] and improvements in stool consistency and diarrhoea outcomes[59,63,64] compared with low-fibre or non-supplemented groups. In contrast, in two studies using low-fibre dietary interventions, one reported no difference in gastrointestinal symptom scores between intervention and standard care groups either during or in the post-treatment setting[61,62] whilst a further study[58] reported improved genitourinary and gastrointestinal symptoms in patients compliant with low-fibre dietary advice amongst a number of other dietary restrictions. Overall, these results indicate that advice to restrict or reduce fibre intake during radiotherapy is outmoded and should be discarded. However, the optimum dose, presentation, fibre source (or substrate) and mechanism of action have yet to be fully elucidated.

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Probiotics, prebiotics and synbiotics

Rationale. Probiotics are live microorganisms (bacteria) that when administered in adequate amounts confer a health benefit on the host[66]. They include (but are not limited to) lactobacilli and bifidobacteria species and remain viable after passage through the human stomach and small intestine. A prebiotic is a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits on host wellbeing and health[67]. Prebiotics include inulin, lactulose and the short-chain carbohydrates fructo-oligosaccharides (oligofructose) and galacto-oligosaccharides. Synbiotics are combinations of probiotics and prebiotics. Prebiotics with ≥3 monomeric units may, according to some European national guidelines, satisfy the definition of fibre[54]. There are a variety of mechanisms through which probiotics exert their health-giving effects. These include modification of the incumbent microbiota population to favour non-pathogenic species, reduction of luminal pH, competitive inhibition of pathogenic strains and secretion of anti-pathogenic compounds, including bacteriocidins and defensins. Probiotics also exert additional beneficial immunomodulatory effects on local mucosal and systemic immune systems[68]. Prebiotics provide a substrate for the preferential growth of non-pathogenic species resulting in the enhanced production of SCFA which promote optimal colonic fluid balance, stimulate water and sodium absorption and preserve mucosal barrier function[55]. Synbiotics offer a potentially synergistic option but differ in efficacy depending on the specific combination.

Evidence. Nine RCT recruiting 1288 patients[69–79] have examined the efficacy of probiotic or synbiotic preparations. Outcomes for the largest study[71] are reported in three separate publications[71,74,75]. All studies are preventative in aim with the exception of one[70]. In the earliest open-label study[69], twenty-four patients were randomised to receive either a synbiotic comprising 2×10^9 (radiation-resistant) *Lactobacillus acidophilus* plus 8 g/d lactulose in addition to a low-fibre, low-lactose, low-fat diet or diet alone. Incidence of diarrhoea was significantly reduced in the synbiotic plus diet group ($P < 0{\cdot}01$) *v.* the diet alone group. The authors postulated that the synbiotic decreased fecal pH and favourably altered fecal microflora, features which had been demonstrated in earlier work that remains unpublished. In a later double-blind (therapeutic) study[70] 206 patients were randomised to receive either a probiotic containing 1·5 g *L. rhamnosis* (equivalent to $1{\cdot}5 \times 10^9$ colony-forming units (CFU)) or placebo to control treatment-induced mild to moderate diarrhoea. No significant difference was found between groups in the time to use of, or frequency of use of rescue medication (Loperamide).

The largest study to date used a double-blind placebo-controlled design to test the efficacy of probiotic cocktail VSL#3 comprising eight different bacterial strains in high concentration (450×10^9 CFU) to reduce treatment induced gastrointestinal toxicity assessed using the WHO five-point grading scale. Earlier reports of the same cohort were published (*n* 190 patients)[74,75] in which it was stated that patients were additionally instructed to follow a hyper-energetic diet (due to radiotherapy-induced metabolic stress) which entailed restricting fat and fructose but maintaining a normal fibre intake[74]. However, it is not clear whether these additional dietary instructions applied to all those recruited for this study. A significantly reduced ($P < 0{\cdot}001$) number of patients in the probiotic group *v.* placebo experienced radiation-induced enteritis and colitis (31·6 *v.* 51·8 %, respectively) with a significantly higher proportion of patients in the placebo group experiencing grade 3 or 4 toxicity ($P < 0{\cdot}001$). Mean daily number of bowel movements for patients with radiation-induced diarrhoea was reduced ($P < 0{\cdot}005$) in the probiotic group *v.* placebo (14·7 (SD 6) *v.* 5·1 (SD 3)) together with significantly reduced ($P < 0{\cdot}001$) mean time to use of Loperamide as rescue medication.

Between 2008 and 2010 results of a further three RCT were published[72,73,76]. In a multi-centre, double-blind study[72], 118 patients with gynaecological cancer were randomly assigned to receive a probiotic drink (10^8 CFU/g *L. casei*) or placebo. This study was originally powered to recruit 154 patients (seventy per group) but only 118 were randomised. Of these, thirty-three patients were subsequently excluded due to ineligibility resulting in only forty-four and forty-one patients in the intervention and placebo groups respectively amounting to only 55 % of those required. Whilst patients in the probiotic group had a significantly improved mean stool consistency ($P = 0{\cdot}04$) including greater median time before experiencing Bristol stool type ≥6 (14 d *v.* ten in the probiotic *v.* placebo, respectively) there was no significant difference between groups in the need for anti-diarrhoeal medication or incidence of Common Terminology Criteria (CTCAE) grade 2 toxicity.

Another study using a double-blind design randomised sixty-three patients with cervical cancer to receive a probiotic preparation (10^9 *L. acidophilus* and 10^9 *Bifidobacterium bifidum*) or placebo starting 7 d prior to radiotherapy and continuing during treatment[73]. Significantly fewer patients in the probiotic group experienced CTCAE grade ≥2 diarrhoea *v.* the placebo group ($P = 0{\cdot}002$). Use of anti-diarrhoeal medication was also significantly reduced in the probiotic group *v.* placebo ($P = 0{\cdot}03$) together with improved stool consistency ($P < 0{\cdot}001$). In the third study completed in this period[76], forty-two patients with mixed pelvic malignancies were randomised to receive either a probiotic preparation or a preparation containing fermentation products during radiotherapy. The probiotic preparation, '5' Strain Dophilus, contained five probiotic cultures in the proportions: 55 % *L. rhamnosus*, 20 % *B. adolescentis*, 5 % *L. acidophilus*, 5 % *B. longum*, 15 % *Enterococcus faecium*, with a total count of six billion active bacteria/capsule at a dose of 2 × 1 capsules daily. The cell-free fermentation product preparation consumed by the comparator group comprised *L. helveticus* and gut symbionts with 100 ml of the product containing: 24·95 g *Escherichia coli* metabolita, 12·5 g *Streptococci faecalis* metabolita, 12·5 g *Lactobacilli acidophili* metabolita, 49·9 g *Lactobacilli helvetici* metabolita) in doses of forty drops, three times daily. The study was not powered for a specific endpoint.

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It was reported that both preparations had beneficial effects on bowel frequency, stool consistency and use of anti-diarrhoeal medication in comparison with previous research and that effects were more marked in the probiotic group[76]. Since 2010, the results of a further three studies have been published[77–79]. It is important to note that during this period radiotherapy techniques have become more sophisticated with more centres now employing image-guided radiotherapy and intensity-modulated radiotherapy. Improved planning and delivery techniques will improve toxicity through the implementation of on-treatment verification protocols (image-guided radiotherapy), the application of smaller margins to allow for uncertainties in radiotherapy delivery and improved dose sculpting to spare normal tissue (intensity-modulated radiotherapy).

In the largest of the trials conducted in this most recent era, 246 patients with mixed pelvic cancers were randomised to receive either placebo or one of two regimens of double-strain Bifilact probiotic (*L. acidophilus* + *B. longum*) at a standard dose (1·3 billion CFU) or high dose (ten billion CFU) during radiotherapy treatment[77]. All received individualised nutritional advice aimed at reducing lipid intake, avoiding caffeine and alcohol and advice on the consumption of dietary fibre. The primary endpoint was time to presentation of ≥grade 2, 3 or 4 diarrhoea. Immediately following radiotherapy treatment (60 d) the proportion of patients free from moderate or severe diarrhoea in the standard dose probiotic group (35 %) was 2-fold higher than that of the placebo group (17 %; $P = 0{\cdot}004$). Further, in a sub-group analysis of patients who had had previous surgery, the standard dose probiotic group had a higher proportion of patients (97 %) without very severe (grade 4) diarrhoea compared with the placebo group (74 %; $P = 0{\cdot}03$). However, the difference between groups in the cumulative proportion of patients without grade 2, 3 or 4 diarrhoea (primary endpoint) was NS ($P = 0{\cdot}13$).

In a much smaller pilot double-blind, placebo-controlled RCT, twenty prostate cancer patients were randomised to receive either a synbiotic powder (*L. reuteri*, 10^8 CFU + 4·3 of soluble fibre) or placebo for 1 week prior to and during radiotherapy[78]. The study was powered to detect a four-point difference between groups in European Organisation for Research and Treatment of Cancer QLQ-PRT23 score. Quality of life + proctitis symptom scores and proctitis symptom scores alone were significantly improved in the probiotic group compared with the placebo group at weeks 2 and 3 of radiotherapy treatment; $P < 0{\cdot}05$ and $< 0{\cdot}01$ for both comparisons at both time-points.

Finally, in the most recent trial[79], sixty-seven patients with mixed pelvic cancers were randomised to receive either a probiotic preparation; probiotic preparation with honey; or placebo for 1 week prior to and during radiotherapy for 5 weeks. The high strength probiotic, was contained within two capsules daily of LactoCareO and comprised: *L. casei* ($1{\cdot}5 \times 10^9$ CFU); *L. acidophilus* ($1{\cdot}5 \times 10^{10}$ CFU); *L. rhamnosus* ($3{\cdot}5 \times 10^9$ CFU); *L. bulgaricus* ($2{\cdot}5 \times 10^8$ CFU); *Bifidobacterium breve* (1×10^{10} CFU); *B. longum* (5×10^8 CFU); *Streptococcus thermophilus* ($1{\cdot}5 \times 10^8$ CFU) per 500 mg, in 150 g low-fat yoghurt. The results revealed significantly reduced frequency (number of bowel movements/d) throughout treatment, reduced diarrhoea grade, improved stool consistency and less need for anti-diarrhoeal medication in either of the probiotic groups at weeks 4 and 5 of treatment compared with the placebo. However, the study lacked statistical power and bloating was noted in nineteen of twenty-two and sixteen of twenty-one patients in the probiotic and probiotic + honey groups respectively *v.* ten of twenty-four patients in the placebo group.

Conclusions. There is mounting evidence that probiotics are helpful as prophylactic agents in reducing the gastrointestinal side effects associated with pelvic radiotherapy. Reported benefits include improved gastrointestinal symptoms[71,73–75,77,78] reduced incidence[69,77] and severity[79] of diarrhoea, reduced need for anti-diarrhoeal medication[71,73–76,79] and improved stool consistency[72,73,76,79] and frequency[71,72,74–76,79]. Despite this seemingly convincing evidence, no single probiotic preparation or dose has yet been recommended for routine clinical practice. The most recent definitive clinical guideline for the prevention of gastrointestinal mucositis in this setting[80] includes a suggestion (based on grade III evidence) arrived at by panel consensus, that probiotics containing *Lactobacillus* species be used to prevent diarrhoea in patients receiving chemotherapy and/or radiation therapy for a pelvic malignancy. Whilst this suggestion reflects the widespread use of this species in research studies and its demonstrated benefits, either alone[69,72,78] or in combination with *Bifidobacteria*[73,77] or with multiple other species[71,74–76,79] no recommendation is made regarding dose; which is no doubt a reflection of the wide variety of strengths that have been used, ranging from $1{\cdot}5 \times 10^9$ to 450×10^9 CFU/ml and the lack of a clear dose–response relationship[77], CFU being the smallest viable unit of the bacteria capable of replication.

Discussion

With the burden of cancer globally doubling between 1975 and 2000 and survival (in the UK) continuing to rise by 3 % per annum[81] it is appropriate to explore strategies to prevent or reduce gastrointestinal toxicity resulting from therapeutic radiotherapy for pelvic cancers. Nutritional interventions represent a low-cost option and many have a sound scientific rationale for use. Thirty original studies have been identified, recruiting over 3000 patients to five major dietary interventions: elemental, low/modified fat, lactose restriction, fibre and probiotic or synbiotic interventions. In general, the dietary interventions were open label due to the acknowledged difficulty of designing sham diets. Many studies also used multiple interventions making it impossible to determine the active component. Study quality was highly variable with many failing to provide details of study powering or analysis of compliance, an essential measure in nutritional interventional research. Added to these uncertainties, it should be noted that the studies

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identified in this review span a period of four decades (1978–2018) during which radiotherapy techniques have improved dramatically with the introduction of conformal, intensity-modulated and image-guided techniques resulting in sparing of normal tissue.

On the basis of the evidence included in this review, there is insufficient high-grade evidence to recommend any of the nutritional interventions assessed to be implemented in clinical practice. However, it seems clear that restrictive dietary practices such as low-lactose, low-fat and low-fibre diets should not be recommended unless a clear clinical rationale is provided or unless their efficacy is being explored within the context of an appropriate clinical trial with appropriate dietetic and immunological monitoring. Total replacement of diet with elemental formula has not been fully trialled and may be more effective than partial replacement but can probably only be achieved after placement of a nasogastric or gastrostomy tube and the evidence does not support its use except in exceptional clinical settings. Whilst one recent study pointed to the efficacy of a high-fibre diet, a dose–response relationship was not observed and manipulating dietary substrates in the clinical setting requires intensive and skilled input from suitably trained personnel.

Of all the interventions assessed in this review probiotic supplementation appears to offer the most promise as a prophylactic for positively influencing toxicity outcomes and is currently the only strategy endorsed within a clinical guideline. However, whilst probiotic supplementation may represent a more easily achievable approach than dietary manipulation, our knowledge about the precise mix of dynamic and diverse microbiota that inhabits the human gut is still very limited and is highly individual. Attempting to manipulate such an ill-defined ecosystem should be approached with caution although our methods of analysing the effects of such supplementation on the incumbent gut microbiota are rapidly improving. Probiotic preparations are of widely differing strengths and combinations and whilst *Lactobacillus* and *Bifidobacteria* have yielded demonstrated benefits, it seems evident that higher doses do not necessarily result in added benefit making it difficult to single out one product over another. Use of concomitant chemotherapy agents during radiotherapy may influence the efficacy of probiotic preparations. Importantly, immunosuppressed patients may respond differently and represent a group of patients at higher risk. In these patients, the use of novel strains should proceed with caution.

After four decades of nutritional intervention research in this setting and no clear 'front runner' we are left with a conundrum as to what dietary recommendations should be given to patients embarking on a course of pelvic radiation therapy? Also, what direction should future research in this area take? Of particular interest in addressing the first of these questions is the work of Ravasco[82,83] which has shown that in both the acute (during radiotherapy) and long-term (median 6·5 years after pelvic radiotherapy) setting, individualised dietary counselling in contrast to *ad libitum* intake or protein supplementation is the most effective strategy for maintaining adequate nutritional status and quality of life. These findings are in keeping with recent research from our group which has shown that an individualised approach to increasing or decreasing fibre intake was of benefit to both groups when compared with *ad libitum* intake[65]. Another small comparator study (*n* 29) indicated that patients following an 'exclusion' as distinct from 'steady diet' experienced significantly worse toxicity, weight loss and quality of life[84] although no details of the intervention are provided. In summary, it seems that an individualised approach, free from restrictive practices with appropriate professional advice (counselling) to manipulate dietary intake based on emerging needs throughout treatment is the way forward. This approach is not without resource implications, notably for dietitians but as Ravasco has elegantly shown, it offers long-term benefits for patients and thereby may also favourably influence associated health service economics.

Future research is likely to focus on the efficacy of probiotics but should employ outcome measures which indicate how the gut microbiota adjusts to the rigours of radiotherapy and the consequences of this adjustment for metabolic products (e.g. SCFA) and the effects on inflammatory processes. If an optimum probiotic prophylactic preparation can be found to protect the gut against dysbiosys (an unfavourable shift in bacterial population dynamics) and ensuing inflammatory processes it would represent a major and cost-effective advance in preventing long-term gastrointestinal morbidity following pelvic radiotherapy.

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Conflicts of Interest

None.

Authorship

The author was solely responsible for all aspects of preparation of this paper.

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