Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers

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[Intervention Review]

Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers

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ABSTRACT

Background

An increasing number of people survive cancer but a significant proportion have gastrointestinal side effects as a result of radiotherapy (RT), which impairs their quality of life (QoL).

Objectives

To determine which prophylactic interventions reduce the incidence, severity or both of adverse gastrointestinal effects among adults receiving radiotherapy to treat primary pelvic cancers.

Search methods

We conducted searches of CENTRAL, MEDLINE, and Embase in September 2016 and updated them on 2 November 2017. We also searched clinical trial registries.

Selection criteria

We included randomised controlled trials (RCTs) of interventions to prevent adverse gastrointestinal effects of pelvic radiotherapy among adults receiving radiotherapy to treat primary pelvic cancers, including radiotherapy techniques, other aspects of radiotherapy delivery, pharmacological interventions and non-pharmacological interventions. Studies needed a sample size of 20 or more participants and needed to evaluate gastrointestinal toxicity outcomes. We excluded studies that evaluated dosimetric parameters only. We also excluded trials of interventions to treat acute gastrointestinal symptoms, trials of altered fractionation and dose escalation schedules, and trials of pre- versus postoperative radiotherapy regimens, to restrict the vast scope of the review.

Data collection and analysis

We used standard Cochrane methodology. We used the random-effects statistical model for all meta-analyses, and the GRADE system to rate the certainty of the evidence.

Main results

We included 92 RCTs involving more than 10,000 men and women undergoing pelvic radiotherapy. Trials involved 44 different interventions, including radiotherapy techniques (11 trials, 4 interventions/comparisons), other aspects of radiotherapy delivery (14 trials, 10 interventions), pharmacological interventions (38 trials, 16 interventions), and non-pharmacological interventions (29 trials, 13 interventions). Most studies (79/92) had design limitations. Thirteen studies had a low risk of bias, 50 studies had an unclear risk of bias and 29 studies had a high risk of bias. Main findings include the following:

Radiotherapy techniques: Intensity-modulated radiotherapy (IMRT) versus 3D conformal RT (3DCRT) may reduce acute (risk ratio (RR) 0.48, 95% confidence interval (CI) 0.26 to 0.88; participants = 444; studies = 4; I^2 = 77%; *low-certainty evidence*) and late gastrointestinal (GI) toxicity grade 2+ (RR 0.37, 95% CI 0.21 to 0.65; participants = 332; studies = 2; I^2 = 0%; *low-certainty evidence*). Conformal RT (3DCRT or IMRT) versus conventional RT reduces acute GI toxicity grade 2+ (RR 0.57, 95% CI 0.40 to 0.82; participants = 307; studies = 2; I^2 = 0%; *high-certainty evidence*) and probably leads to less late GI toxicity grade 2+ (RR 0.49, 95% CI 0.22 to 1.09; participants = 517; studies = 3; I^2 = 44%; *moderate-certainty evidence*). When brachytherapy (BT) is used instead of external beam radiotherapy (EBRT) in early endometrial cancer, evidence indicates that it reduces acute GI toxicity (grade 2+) (RR 0.02, 95% CI 0.00 to 0.18; participants = 423; studies = 1; *high-certainty evidence*).

Other aspects of radiotherapy delivery: There is probably little or no difference in acute GI toxicity grade 2+ with reduced radiation dose volume (RR 1.21, 95% CI 0.81 to 1.81; participants = 211; studies = 1; *moderate-certainty evidence*) and maybe no difference in late GI toxicity grade 2+ (RR 1.02, 95% CI 0.15 to 6.97; participants = 107; studies = 1; *low-certainty evidence*). Evening delivery of RT may reduce acute GI toxicity (diarrhoea) grade 2+ during RT compared with morning delivery of RT (RR 0.51, 95% CI 0.34 to 0.76; participants = 294; studies = 2; I^2 = 0%; *low-certainty evidence*). There may be no difference in acute (RR 2.22, 95% CI 0.62 to 7.93, participants = 110; studies = 1) and late GI toxicity grade 2+ (RR 0.44, 95% CI 0.12 to 1.65; participants = 81; studies = 1) between a bladder volume preparation of 1080 mls and that of 540 mls (*low-certainty evidence*). Low-certainty evidence on balloon and hydrogel spacers suggests that these interventions for prostate cancer RT may make little or no difference to GI outcomes.

Pharmacological interventions: Evidence for any beneficial effects of aminosalicylates, sucralfate, amifostine, corticosteroid enemas, bile acid sequestrants, famotidine and selenium is of a low or very low certainty. However, evidence on certain aminosalicylates (mesalazine, olsalazine), misoprostol suppositories, oral magnesium oxide and octreotide injections suggests that these agents may worsen GI symptoms, such as diarrhoea or rectal bleeding.

Non-pharmacological interventions: Low-certainty evidence suggests that protein supplements (RR 0.23, 95% CI 0.07 to 0.74; participants = 74; studies = 1), dietary counselling (RR 0.04, 95% CI 0.00 to 0.60; participants = 74; studies = 1) and probiotics (RR 0.43, 95% CI 0.22 to 0.82; participants = 923; studies = 5; I^2 = 91%) may reduce acute RT-related diarrhoea (grade 2+). Dietary counselling may also reduce diarrhoeal symptoms in the long term (at five years, RR 0.05, 95% CI 0.00 to 0.78; participants = 61; studies = 1). Low-certainty evidence from one study (108 participants) suggests that a high-fibre diet may have a beneficial effect on GI symptoms (mean difference (MD) 6.10, 95% CI 1.71 to 10.49) and quality of life (MD 20.50, 95% CI 9.97 to 31.03) at one year. High-certainty evidence indicates that glutamine supplements do not prevent RT-induced diarrhoea. Evidence on various other non-pharmacological interventions, such as green tea tablets, is lacking.

Quality of life was rarely and inconsistently reported across included studies, and the available data were seldom adequate for meta-analysis.

Authors' conclusions

Conformal radiotherapy techniques are an improvement on older radiotherapy techniques. IMRT may be better than 3DCRT in terms of GI toxicity, but the evidence to support this is uncertain. There is no high-quality evidence to support the use of any other prophylactic intervention evaluated. However, evidence on some potential interventions shows that they probably have no role to play in reducing RT-related GI toxicity. More RCTs are needed for interventions with limited evidence suggesting potential benefits.

PLAIN LANGUAGE SUMMARY

Interventions to reduce digestive side effects of pelvic x-ray treatment

Background

Radiotherapy (RT: x-ray treatment) is a common anti-cancer treatment that often cures people of their cancer, but can damage the gastrointestinal (digestive) tract and lead to distressing short-term (acute) and long-term (late) gastrointestinal side effects, which can start many months or years after the radiotherapy has finished. These side effects, such as diarrhoea, faecal urgency (a sudden need to pass stool), and faecal incontinence (leakage of stool from the rectum) can damage a person's quality of life (QoL). We conducted this review to establish whether there are any treatments that can be given to people undergoing pelvic radiotherapy (RT) to reduce gastrointestinal side effects.

Methods

We searched the medical literature up to 2 November 2017 and selected randomised controlled trials (RCTs) of any preventive treatment (intervention) given to people undergoing RT for pelvic cancer (such as bladder, endometrial, cervix, rectum and prostate cancers). We combined data from similar RCTs to provide a summary estimate of the effect of an intervention and made a judgement about how confident (certain) we are of the findings, using established methods (GRADE).

Results

We identified 92 RCTs involving 44 different interventions to reduce RT-related gastrointestinal side effects. These included new methods (RT techniques) and other aspects of delivering RT (lower RT dosages, different bladder volumes, morning or evening RT delivery, injected gels or rectally-inserted balloons (spacers] to protect the rectum, and other options), drugs (aminosalicylates, amifostine, corticosteroids, famotidine, octreotide, magnesium oxide, misoprostol, selenium, sodium butyrate, smectite, sucralfate, superoxide dismutase), and non-drug treatments (different types of diets, glutamine, counselling, green tea, and other options). We found some evidence to show that certain interventions have no role to play in reducing gastrointestinal side effects (particularly glutamine supplements, misoprostol suppositories, oral magnesium oxide and octreotide injections). However, we found little good evidence (moderate or high certainty) to show that any of the options is helpful. The exceptions to this are the evidence on RT techniques, which shows that conformal (modern) RT techniques are better than older RT techniques, and evidence that vaginal brachytherapy (small radioactive balls placed in the vagina) for early endometrial cancer reduces acute gastrointestinal side effects compared with external-beam radiotherapy.

Conclusions

Modern (conformal) RT methods are helpful in reducing RT-related side effects. There is insufficient evidence to robustly support the use of any single drug or non-drug option or other RT delivery device/option to reduce RT-related gastrointestinal effects. More high-quality research is needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Conformal RT compared with conventional RT to reduce adverse GI effects of radiotherapy

Patient or population: People with urological (prostate) gynaecological (cervical) cancer
Settings: Tertiary care setting
Intervention: Conformal RT (3DCRT and IMRT)
Comparison: Conventional RT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional RT	Conformal RT (3DCRT and IMRT)				
Mean GI symptom scores	-	-	Not estimable	0	-	No data
Acute and late GI toxicity grade 2+	Acute toxicity (up to 3 months post-RT): **365 per 1000**	Acute toxicity (up to 3 months post-RT): **208 per 1000** (146 to 299)	**RR 0.57** (0.40 to 0.82)	307 (2)	⊕⊕⊕⊕ **high**	The effects in 3DCRT and IMRT subgroups were consistent with the overall effect estimate
	Late toxicity (from 6 months post-RT): **155 per 1000**	Late toxicity (from 6 months post-RT): **76 per 1000** (34 to 171)	**RR 0.49** (0.22 to 1.09)	517 (3)	⊕⊕⊕◯ **moderate**[1]	The effects in 3DCRT and IMRT subgroups were consistent with the overall effect estimate but there was substantial heterogeneity within the 3DCRT subgroup (I^2 = 60%)
Diarrhoea (grade 2+)	-	-	Not estimable	0	-	No data
QoL scores	-	-	Not estimable	0	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision (wide confidence interval crossing the line of no effect).

BACKGROUND

Description of the condition

In 2012, 14.1 million people worldwide were diagnosed with cancer and 32.6 million people were living with cancer (within five years of diagnosis) (GLOBOCAN 2012). The number of people surviving cancer has increased significantly over the past few decades, due to earlier diagnosis and advances in multimodal treatment (Andreyev 2012; Cancer Res 2016). Radiotherapy (RT) is a key component of anti-cancer treatment and approximately four out of every 10 people with cancer have radiotherapy as part of their treatment (Cancer Res 2016). Whilst anti-cancer treatment is not always curative, it enables many people with a diagnosis of cancer to live for significantly extended periods.

Pelvic radiotherapy is used to treat various urological, gynaecological and gastrointestinal cancers, where it might be given alone as primary treatment, combined with chemotherapy, or given before or after surgery. During treatment, pelvic radiotherapy inevitably exposes the surrounding normal gastrointestinal tract (small and large bowel) to some degree of radiation. Depending on various factors, such as the type of radiotherapy, the size and site of the treatment field, and the dose delivered, irradiation of normal tissue can lead to bowel injury (Andreyev 2007). In addition, other factors may influence the risk of bowel injury, including chemotherapy, previous abdominal surgery, smoking, co-existing medical conditions or their treatments (such as diabetes, hypertension and HIV), concurrent medication, genetic factors, and psychological issues (Andreyev 2007; Theis 2010).

Pelvic radiation disease (PRD), the term used for non-cancerous tissue injury secondary to radiotherapy, is increasingly being recognised as an unacceptable consequence of radiotherapy treatment (Morris 2015). Radiation-induced gastrointestinal tissue injury is brought about initially by an acute inflammatory process that leads to blood vessel damage, ischaemia (inadequate blood supply to the tissue), fibrosis (thickening and scarring), and loss of stem cells (Denham 2002). With repeated exposures over the course of radiotherapy treatment, the cycle of tissue injury and disrupted healing leads to progressive alteration in the affected tissue architecture and function. Gastrointestinal symptoms can be acute (occurring during radiotherapy or within three months), or chronic (persisting or appearing after three months) (Frazzoni 2015). Acute symptoms, including diarrhoea, abdominal pain, nausea, bloating, rectal bleeding, and urgency, typically begin during the second week of treatment and peak at four to five weeks (Khalid 2006). Acute symptoms usually resolve upon cessation of radiotherapy; however, they can necessitate dose reductions and treatment interruption, which can have a negative impact on the curative effect of treatment (Morris 2015; Stacey 2014). In addition, their occurrence may increase the risk of late gastrointestinal effects (Barnett 2011; O'Brien 2002). Chronic symptoms, including faecal incontinence, urgency, rectal bleeding, flatulence, and abdominal pain, can follow acute symptoms or arise on their own some time later (Andreyev 2012). Incontinence can be particularly distressing and may be caused by injury to the anal sphincter and rectal tissue, leading to decreased rectal distensibility and storage capacity (Krol 2014). However, as widely-separate parts of the gastrointestinal tract that lie in the path of the radiotherapy beam can be affected, symptoms associated with injury can have more than one physiological cause (Andreyev 2007). In addition, bile acid malabsorption, carbohydrate intolerances, and small bowel bacterial overgrowth occurring as a result of radiation-induced impaired bowel motility may exacerbate bowel symptoms (Andreyev 2007; Muls 2014). Chronic symptoms are very common, with up to 90% of patients reporting a permanent change in their bowel habits (Olopade 2005), and up to 30%, 40% and 66% respectively of urological, gynaecological and colorectal cancer survivors experiencing chronic gastrointestinal symptoms that negatively affect their quality of life (Andreyev 2012). Rarely, severe intestinal failure can occur as a result of RT damage; furthermore, RT-exposed intestine has an increased risk of needing surgery (Gavazzi 2006; Kalaiselvan 2014).

Description of the intervention

Radiotherapy is a cancer treatment involving the use of high-energy radiation, usually x-rays or similar beams (such as electrons or protons), to destroy cancer cells. The aim of modern radiotherapy is to ensure a high level of accuracy in tumour targeting, to reduce normal tissue exposure, and to minimise side effects (NCAT 2012). A variety of different strategies have been proposed to reduce its impact on normal tissues and prevent adverse gastrointestinal effects. These include improved radiotherapy delivery techniques, other aspects of radiotherapy delivery (e.g. timing of delivery, patient positioning or positioning devices), pharmacological interventions, and non-pharmacological interventions:

Radiotherapy delivery techniques

Conventional radiotherapy is delivered as external beam radiotherapy (EBRT). Conformal radiotherapy is the type of EBRT that is commonly used in high-income countries (Cancer Res 2016; CCS 2016). There are two types:

- 3D conformal radiotherapy (3DCRT) is intended to improve tumour targeting and reduce the amount of radiation to the surrounding tissues by aiming shaped radiotherapy beams from several different directions at the tumour (CCS 2016). It uses pretreatment imaging with computerised tomography (CT) or other types of scans to plan the radiotherapy treatment area in three dimensions (width, height and depth), matching the radiation beams to the 3D shape of the tumour. With 3DCRT, the radiation beams are all the same intensity;
- Intensity-modulated radiotherapy (IMRT) uses computerised methods to orientate multiple small beams of

different intensities to the volume of tumour tissue that needs to be treated (Cancer Res 2016; NCAT 2012). IMRT may potentially conform more precisely to the tumour than 3DCRT, as it allows the dose of radiation to be adjusted for different parts of the treatment area and can create concave edges to reduce exposure to adjacent normal tissues. Volumetric modulated arc therapy (VMAT) is a type of IMRT in which the machine rotates around the patient during treatment, continuously adapting the radiation beam to the tumour volume as it moves.

All radiation doses quoted in this review assume a fraction size of 1.8 to 2.0 Gy, unless otherwise stated. It is currently unclear whether the occurrence or severity of adverse gastrointestinal effects in patients undergoing radiotherapy differ between these techniques.

Image-guided radiotherapy (IGRT)

IGRT includes any imaging performed at pretreatment and treatment delivery that improves or verifies the accuracy of radiotherapy (NCAT 2012). It encompasses a wide variety of techniques ranging from simple visual field alignment checks through to CT imaging that enables direct visualisation of the radiotherapy target volume and surrounding anatomy (NCAT 2012). If sufficiently accurate, IGRT has the potential to allow a reduction in the setup margin for a particular cancer site, reducing the radiation exposure to normal tissue. Four-dimensional adaptive radiotherapy (4D-ART) combines IMRT and IGRT to take into account the 3D tumour shape over time (the fourth dimension) by tracking tumour motion during treatment (NCAT 2012).

Stereotactic body radiotherapy (SBRT)

SBRT involves the use of a high and precise radiation dose in a small number of fractions (NCAT 2012). Radiotherapy beams are orientated from many different positions around the body to minimise the radiation dose to the surrounding tissues (Cancer Res 2016). SBRT is currently mainly used for small tumours of the brain, liver, lung and spinal cord; however, its use could potentially be extended to prostate cancer (Lischalk 2016; Moon 2017).

Brachytherapy (BT)

BT involves the placement of radioactive seeds within the tumour (interstitial brachytherapy), or within a cavity adjacent to the tumour (intracavitary brachytherapy) (Shadad 2013). Irradiation may be over a prolonged period of time (low dose) or temporary and short-term (high dose). BT is often used in combination with EBRT. Where evaluated as an alternative to EBRT-based treatments, it has been associated with lower gastrointestinal toxicity (Nout 2010; Sorbe 2012).

Gastrointestinal injury is more likely with higher prescribed radiation doses (Barnett 2011; Michalski 2010). Therefore, limiting the volume of normal tissue exposed to intermediate (45 to 60 Gy) and high doses (60 or more Gy) by using dose-volume constraints is an important part of treatment planning (Michalski 2010). Such parameters need adaptation and validation for different EBRT techniques (Michalski 2010). Irrespective of the radiotherapy technique used, effective immobilisation both in the patient's bony anatomy and of internal organ motion during treatment is critical to avoid 'geographical miss', which will underdose the tumour and overdose the surrounding normal tissues (NCAT 2012).

Other aspects of radiotherapy delivery

Patient positioning or positioning devices

The position of a patient during radiotherapy delivery might influence the dose of radiation delivered to normal pelvic structures and subsequent gastrointestinal injury. A systematic review of prospective and retrospective studies of patient positioning and the use of belly boards suggests that delivering radiotherapy to patients positioned in the prone position (lying on their front) rather that the supine position (lying on their back), and using positioning devices such as belly boards, might facilitate displacement of the small bowel away from the treatment field and reduce the volume of small bowel irradiated (Weisendanger-Wittmer 2012).

Timing of delivery

Physiological 'clocks' that regulate the timing of physiological processes through gene expression exist in every organ and cell of the human body (Fuhr 2015). The circadian clock or day-night cycle is the core clock that might influence response to anti-cancer treatments and the development of treatment side effects (Fuhr 2015). It has been suggested that radiotherapy delivered in the morning may be more likely to cause damage to gastrointestinal mucosal cells than radiotherapy delivered in the evening, due to limited evidence that gastrointestinal cellular proliferation follows a circadian rhythm, with bowel mucosal proliferation (DNA synthesis) being greatest in the morning and lowest in the evening (Buchi 1991; Ijiri 1990).

Fractionation

Curative pelvic radiotherapy treatment comprises a number of doses or fractions (usually 2 Gy or less per fraction), usually given over a period of about four to eight weeks to make up the total prescribed radiotherapy dose. Certain cancers such as prostate cancer have been shown to be more sensitive to fraction size than other tumours, behaving more like normal tissues; therefore, increasing the fraction size (hypofractionation) for each treatment, which allows the total dose to be delivered in fewer treatments, might improve the treatment outcome or therapeutic ratio (Bossi 2016; Soh 2015). Several randomised trials of hypofractionation in prostate cancer have been conducted (Aluwini 2015; Arcangeli

2010; CHHiP 2016; Hoffman 2014; Norkus 2013; Pollack 2013). A 2015 systematic review concludes that moderate fractionation (2.5 to 4 Gy per fraction) is associated with late gastrointestinal toxicity similar to conventional fractionation; however, extreme fractionation (5 to 10 Gy per fraction) may have greater toxicity than conventional fractionation (Koontz 2015). Whilst potential benefits of hypofractionation include patient convenience, reduced treatment time and cost reduction (Moon 2017; Soh 2015), hypofractionation is not expected to reduce toxicity and might increase it; most trials of hypofractionation therefore hope to show that it is safe and non-inferior to conventional fractionation in terms of toxicity. We therefore consider interventions dealing with altered fractionation schedules to be outside the scope of this review. A separate Cochrane Review to evaluate the efficacy and toxicity of altered fractionation schedules for prostate cancer is currently underway (Soh 2015).

Other interventions

Various surgical techniques have been proposed, such as the surgical placement of absorbable mesh slings to exclude the small bowel from the field of radiation, to reduce the gastrointestinal effects of pelvic radiotherapy (Devereux 1988; Rodier 1991); however, the clinical effectiveness of such techniques remains uncertain (Stacey 2014). Using daily endorectal balloons filled with air or water, which aim to reduce the volume of normal tissues being irradiated, might be beneficial for men undergoing prostate radiotherapy; findings from a non-Cochrane review suggest that such devices might reduce prostate motion, improve dosimetry and reduce early gastrointestinal toxicity (Both 2012). Similarly, gel or balloon spacers inserted into the prerectal space before RT might protect the rectum from adverse effects of this treatment.

Pharmacological interventions

Mucosal protectants

Drugs that might protect the mucosa of the gastrointestinal tract from damage due to pelvic radiotherapy include sucralfate (a sucrose sulfate-aluminium complex) and various agents with antioxidant properties:

- Sucralfate binds to tissue proteins, creating a physical barrier over damaged mucosal surfaces and facilitating epithelial healing (Van de Wetering 2016). Low- to moderate-certainty Cochrane evidence suggests that it may be useful in the treatment of acute radiation-induced rectal bleeding, but it remains unclear whether it can prevent rectal bleeding or other gastrointestinal symptoms of PRD when administered prophylactically (Van de Wetering 2016).
- Amifostine is thought to mediate a protective effect within normal cells by free-radical scavenging, DNA protection and repair acceleration, and induction of cellular hypoxia (Kouvaris 2007). It is used to protect renal cells from the effects of platinum chemotherapy in ovarian cancer, and in people undergoing radiotherapy for head and neck cancers to reduce xerostomia (dryness of the mouth) (Kouvaris 2007).
- Antioxidants, such as vitamins C, D, and E, might reduce radiotherapy-induced injury by reducing antioxidant stress within gastrointestinal cells and facilitating tissue repair. Glutamine, a non-essential amino acid, selenium, and other agents with antioxidant properties could also potentially be protective (Hall 2016).

Anti-inflammatory agents

5-aminosalicylates (e.g. sulfasalazine, balsalazide) are used in the treatment of certain inflammatory bowel conditions, e.g. ulcerative colitis, and therefore might have a role in preventing acute inflammatory gastrointestinal effects of radiation, as suggested by the findings of some small trials (Jahraus 2005; Kilic 2001). Other anti-inflammatory agents that could potentially reduce gastrointestinal damage include other nonsteroidal anti-inflammatories and corticosteroids.

Statins (3-hydroxy-methylglutaryl coenzyme-a reductase inhibitors) and angiotensin-converting enzyme (ACE) inhibitors

A retrospective study of the effects of statins and ACE inhibitors on gastrointestinal effects in a cohort of people undergoing radiotherapy for pelvic malignancies reported better acute and long-term gastrointestinal symptom scores among those receiving statins (with or without ACE inhibitors) (Wedlake 2012); however, retrospective studies have a high risk of bias. Theoretically, statins might counteract some effects of radiation on normal tissues, due to their vasculoprotective properties (Wang 2007).

Other agents

Octreotide is an analogue of the hypothalamic release-inhibiting hormone somatostatin (BNF 2016). It is mainly used to relieve diarrhoeal symptoms associated with neuroendocrine tumours, but it may have a role to play in reducing chemoradiotherapy-related diarrhoea, through inhibitory effects on gastrointestinal secretions and hormones, and on gastrointestinal motility (Sun 2014; Yavuz 2002). However, weak evidence from a 2014 review of octreotide (given subcutaneously or intramuscularly) compared with placebo among people undergoing chemotherapy or radiotherapy suggests that octreotide might reduce diarrhoea when used therapeutically but not preventively in this context (Sun 2014). Various other pharmacological agents, such as bile acid sequestrants (e.g. cholestyramine), sodium butyrate, and smectite, have also been investigated. Bile acid sequestrants act by binding bile acids, which are normally reabsorbed in the terminal ileum and might cause diarrhoea if reabsorption is disrupted, for example,

by radiotherapy-induced dysfunction (Stryker 1983). Sodium butyrate is a short chain fatty acid that has been shown to have anti-inflammatory properties and trophic effects on colonic mucosa (Maggio 2014); and smectite is a natural aluminomagnesium clay that has anti-diarrhoeal properties (Dupont 2009).

Non-pharmacological interventions

Probiotics

Probiotic preparations contain live and defined micro-organisms (usually lactobacilli and bifidobacteria) which, when administered in sufficiently large amounts, alter the host's microflora and potentially confer a health benefit (Kligler 2008). The potential mechanism/s of action of probiotics include epithelial cell proliferation, enhancing secretion of protective mucins, inhibiting bacterial translocation and stimulating the immune response (Van de Wetering 2013). Several clinical studies have investigated the role of probiotics for radiation-induced gastrointestinal injury, but the role of probiotics in preventing or reducing PRD remains uncertain (Stacey 2014; Wedlake 2013).

Nutritional interventions

Malnutrition can occur as a consequence of radiotherapy-induced impaired gastrointestinal absorption and digestive functioning, and can also influence the development of gastrointestinal toxicity (Henson 2013). A 2013 Cochrane Review evaluated the evidence for various nutritional interventions in improving the nutritional status of people undergoing radiotherapy, and found that dietary modification of fat, lactose, or non-starch polysaccharides (fibre) intake, or combinations of these dietary modifications, probably reduces diarrhoea at the end of radiotherapy (Henson 2013). However, another review concluded that there was insufficient evidence on nutritional interventions to guide clinical practice (Wedlake 2013).

Why it is important to do this review

The focus of cancer and anti-cancer treatment is usually on survival. However, an increasing number of people survive cancer and can develop distressing side effects as a result of treatment. The impact of treatment on the cancer survivor's quality of life has been a much-neglected area of research in cancer treatment. In addition, clinicians tend to focus on ruling out cancer recurrence and progression at follow-up appointments, rather than asking about and addressing quality-of-life-related symptoms. These factors together suggest to cancer survivors that the side effects of radiotherapy treatment are a necessary trade-off against survival. Those affected may therefore be embarrassed to discuss their gastrointestinal symptoms with healthcare professionals, may delay seeking help for them, and may try to manage these problems themselves (Muls 2014).

To our knowledge, there is no comprehensive systematic review of prophylactic interventions to reduce the gastrointestinal toxicity of radiotherapy. Systematic reviews of endorectal balloons (Both 2012), patient positioning (Weisendanger-Wittmer 2012) and IMRT (Yu 2016) have included prospective and retrospective studies and have not graded the quality or certainty of evidence; two systematic reviews on nutritional interventions have reached slightly different conclusions (Henson 2013; Wedlake 2013); a systematic review of octreotide pooled data from prevention and treatment studies (Sun 2014), and a Cochrane Review of selenium supplements is out of date (Dennert 2006). These factors make interpretation of existing evidence difficult. The aim of this review is therefore to systematically and critically appraise the evidence from randomised controlled trials on prophylactic interventions that might reduce the incidence or severity of gastrointestinal symptoms caused by pelvic radiotherapy, and to bring them all together in one comprehensive review, in order to highlight those interventions that will lead to improvements in the quality of life of cancer survivors, and to direct the much-needed research in this field.

OBJECTIVES

To determine which prophylactic interventions reduce the incidence, severity, or both of adverse gastrointestinal effects among adults receiving radiotherapy to treat primary pelvic cancers.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). We excluded quasi-RCTs and cross-over designs.

Types of participants

Adults aged 18 years and older undergoing primary, adjuvant or neoadjuvant radiotherapy as part of anti-cancer treatment for primary pelvic cancers, including urological, gynaecological and gastrointestinal (GI) cancers. We excluded studies of participants receiving palliative radiotherapy or radiotherapy for recurrent cancer, and studies of participants with stomas. Where we found studies that include mixed groups that include some ineligible participants, we attempted to extract data for the relevant participant

subgroups only. If this was not possible, we included the study if at least 80% of the participants were eligible, and indicated our concerns related to the types of participants in the 'Risk of bias' assessment of the study. We excluded studies in which fewer than 80% of participants were eligible. Included studies needed to include at least 20 participants.

Types of interventions

Interventions to prevent adverse gastrointestinal effects of pelvic radiotherapy, including:

- Radiotherapy techniques (e.g. 3DCRT, IMRT, BT);
- Interventions related to radiotherapy delivery, including radiotherapy timing (e.g. evening radiotherapy schedules), patient positioning and positioning devices (e.g. belly boards), and other interventions (e.g. endorectal balloons);
- Pharmacological interventions (e.g. sucralfate, 5-aminosalicylates, antioxidants, statins, ACE inhibitors);
- Non-pharmacological interventions, including dietary modification of macronutrients (carbohydrate, fats, protein, with or without micronutrients) and/or non-starch polysaccharides (dietary fibre), probiotics, and other interventions.

Comparators for radiotherapy techniques or timing are other radiotherapy techniques or timing, whereas comparators for other types of interventions are placebos, no intervention, or alternative interventions. We excluded trials of interventions to treat patients with acute symptoms, as these are not preventive interventions in the first instance. We also excluded trials of altered fractionation and dose escalation schedules, and trials of pre- versus postoperative radiotherapy regimens.

Types of outcome measures

Included studies needed to evaluate gastrointestinal toxicity.

Primary outcomes

1. Gastrointestinal symptom score, according to the Inflammatory Bowel Disease Questionnaire-bowel function dimension (IBDQ-BD), Gastrointestinal Symptom Rating Scale (GSRS), or another scale.
2. Moderate or severe GI symptoms (toxicity), according to the Common Terminology Criteria for Adverse Events (CTCAE 2010), European Organisation for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) scoring system, IBDQ, GSRS, or another scale, including:
    - Overall GI symptoms (grade 2+ toxicity);
    - Diarrhoea (the passing of frequent, loose stool);
    - Faecal incontinence (leakage of stool from the rectum);
    - Faecal urgency (a sudden, almost uncontrollable, need to pass stool);
    - Rectal bleeding;
    - Tenesmus (a feeling of incomplete evacuation and a constant urge to pass stool);
    - Abdominal pain/cramps;
    - Nausea;
    - Vomiting;
    - Flatulence;
    - Weight loss.
3. Quality of life (QoL) score, according to EORTC QLQ-C30, QLQ-PR25, Prostate Cancer Quality of Life Scale (PC-QOL), IBDQ or another scale.

We assessed these outcomes at specific time points to reflect acute (during and up to three months after radiotherapy) and late (six months post-radiotherapy and longer) effects.

Secondary outcomes

1. GI toxicity grade 1+;
2. Toxicity-related discontinuation;
3. Medication use for GI symptom control;
4. Patient satisfaction (as measured by investigators);
5. Total mean bowel dose (Gy) (for studies evaluating radiotherapy techniques, patient positioning or positioning devices).

We excluded studies that evaluated dosimetric parameters only.

Search methods for identification of studies

Electronic searches

We searched the following databases up to September 2016:

- Cochrane Central Register of Controlled Trials (CENTRAL): Issue 9, 2016
- MEDLINE: 1946 to September Week 3 2016
- Embase: 1980 to 2016 week 39

In November 2017, we updated the search as follows:

- CENTRAL: Issue 11, 2017
- MEDLINE: September 2016 to October Week 4, 2017
- Embase: September 2016 to 2017 week 44

We present the CENTRAL, MEDLINE and Embase search strategies in Appendix 1, Appendix 2. Appendix 3 respectively.
We did not apply language restrictions to any of the searches.

Searching other resources

We searched the following databases for ongoing trials:

- ClinicalTrials.gov (clinicaltrials.gov/)
- International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/)

If we found ongoing trials that had not been published through these searches, we approached the principal investigators for an

update on the trial status. We tabulated details of the ongoing trials, including any information acquired from investigators on the trial status, in the Characteristics of ongoing studies section of the review.

We used the 'Related articles' feature of PubMed and the reference lists of included studies to identify newly-published articles and relevant additional studies. We did not handsearch conference proceedings for conference abstracts due to resource limitations and because we considered that we would find most relevant records by the electronic searches, so that any additional yield would be negligible. See Potential biases in the review process for comment on handsearching.

Data collection and analysis

Selection of studies

The Information Specialist at the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group downloaded all titles and abstracts retrieved by electronic searching to Endnote and removed duplicates and those studies that clearly did not meet the inclusion criteria. Two review authors (Theresa Lawrie (TL) and John Green (JG)) independently screened the remaining records by title and abstract using Covidence (www.covidence.org/). We obtained the full texts of the short list of potentially eligible references. TL and JG independently assessed the eligibility of the full-text records, with the help of a third review author (Mark Beresford (MB)), who assisted when necessary to resolve disagreements and uncertainties. We documented the reasons for exclusion of all excluded studies.

Data extraction and management

Two review authors (from TL, JG, MB, Susan Davidson (SD), Linda Wedlake (LW) and Sorrel Burden (SB)) independently extracted data from included studies to a predesigned Excel® data extraction form, to include the following:

- Author contact details;
- Country;
- Setting;
- Funding source;
- Inclusion and exclusion criteria;
- Study design, methodology;
- Study population and baseline characteristics:
    - Number of participants enrolled;
    - Number of participants analysed;
    - Mean (SD) or median (range) age of participants;
    - Numbers of male and female participants;
    - Number of participants with urological, gynaecological, colorectal, and other cancer;
    - Number of participants who received primary, adjuvant, or neoadjuvant radiotherapy;
    - Other anti-cancer treatment;
    - Radiotherapy type, total dose and dose-volume;
    - Baseline gastrointestinal symptoms.
- Intervention details:
- ○ Type of intervention, i.e. radiotherapy techniques, pharmacological interventions, treatment schedules, patient positioning and positioning devices, nutritional and other interventions, including dose, frequency, and timing;
    - Type of comparator, e.g. other intervention, no active intervention (observation or placebo).
- Risk of bias in study (see below);
- Duration of follow-up;
- Study outcomes;
- Review outcomes:
    - time point/s for collection;
    - type of scale used, scale thresholds used for determining severity of symptoms;
    - For dichotomous outcomes (e.g. number of participants with moderate or severe gastrointestinal symptoms), the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at the time point;
    - For continuous outcomes (e.g. QoL scores), the value and standard deviation of the outcome of interest and the number of participants assessed at the relevant time point in each treatment arm. We also extracted change-from-baseline score data where reported;
    - Where possible, all data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in the groups to which they were assigned. We resolved differences between review authors by discussion or by appeal to a third review author when necessary;
    - We anticipated inter-study heterogeneity in the measurement and reporting of gastrointestinal symptoms. We therefore prespecified that we would consider acute and late GI effects to be 'severe' if they were classified as grade 3 or higher according to CTCAE or EORTC RTOG criteria, or determined to be 'severe' by investigators according to investigator-interview or self-report questionnaires, such as the Gastrointestinal Symptom Rating Scale (GSRS). Similarly, we considered 'moderate' GI effects to be the equivalent of CTCAE or RTOG grade 2 assessments or as determined by investigators according to the measurement scale used, and 'mild' effects to be the equivalent of grade 1 (Table 1). In the event that symptom events were reported but not graded, we extracted the available symptom data from the report and noted the potential risk of bias for these data.

Assessment of risk of bias in included studies

We assessed the risks of bias of included studies using Cochrane's tool and the criteria specified in the *Cochrane Handbook for Sys-*

tematic Reviews of Interventions (Higgins 2011). This included assessment of:

- random sequence generation;
- allocation concealment;
- blinding of participants and healthcare providers;
- blinding of outcome assessors;
- incomplete outcome data;
- selective reporting of outcomes;
- other possible sources of bias;
- overall judgement.

For details, see Appendix 4.

Blinding of participants and healthcare providers was not feasible for certain interventions, e.g. radiotherapy techniques or patient positioning. If we rated a study at high risk of bias for this domain due to a lack of this type of blinding, but at low or unclear risk for the other domains, we usually judged the study to be at low or unclear risk of bias overall. Several outcomes were measured by self-reported scales. In general, we did not consider self-reported symptom and QoL outcomes to represent a high risk of bias in the context of this review, as these were our primary outcomes. However, where the outcome had been investigator-assessed and where the investigator had been non-blind (i.e. aware of the group allocation), we assessed the study as being at high risk of bias for the 'blinding of outcome assessor' domain and at a potentially high risk of bias overall, depending on the other risk-of-bias judgements.

Two review authors applied the 'Risk of bias' tool independently and resolved differences by discussion or by appeal to a third review author. We summarised judgements in 'Risk of bias' tables along with the characteristics of the included studies. We interpreted results of meta-analyses in light of the overall risk-of-bias assessment.

Measures of treatment effect

- For dichotomous outcomes (e.g. incidence of acute GI toxicity), we calculated the effect size as a risk ratio (RR) with its 95% confidence interval (CI).
- For continuous outcomes (e.g. QoL scores) we assumed that study authors would use different measurement scales and estimated the standardised mean difference (SMD) and its 95% CI using the pooled data in this instance. However, if the same measurement scale was used, we estimated the mean difference (MD) and its 95% CI. In the event that studies did not report total values but instead reported change-from-baseline outcomes, we would have combined these change values with total measurement outcomes by using the (unstandardised) mean difference method in Review Manager 5 (RevMan) (RevMan 2014). We planned to use subgroups to distinguish between MDs of change scores and MDs of final values, and to pool the subgroups in an overall analysis where data were reported in both of these ways (Higgins 2011). However, this scenario did not occur.
- We did not use time-to-event data.

Unit of analysis issues

Two review authors (TL and JG or MB) reviewed unit of analysis issues according to Higgins 2011 and resolved differences by discussion. These included reports where:

- There were multiple observations for the same outcome (e.g. repeated measurements with different scales or at different time points, recurring events).

We have discussed the implications of our unit of analysis decisions in the section on 'Potential biases in the review process' in the Discussion.

Dealing with missing data

We did not impute missing data. In the event of missing data, such as missing standard deviations or individual outcome denominators, where possible, we attempted to derive these data using calculations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Despite various attempts to contact study authors to request missing data, we could not obtain any study data in this way. We described in the Characteristics of included studies tables how we acquired any missing data. Where denominators were estimated we reflected this limitation in the 'Risk of bias' table for the study concerned and in the subsequent grading of the evidence.

Assessment of heterogeneity

We assessed heterogeneity between studies in each meta-analysis by visual inspection of forest plots, by estimation of the percentage of heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001), and, where possible, by subgroup analyses. If there was evidence of substantial heterogeneity (I^2>60%), we investigated and reported the possible reasons for this.

Assessment of reporting biases

We had planned to investigate reporting biases if there were 10 or more studies in meta-analyses using funnel plots, but all meta-analyses included fewer than 10 studies. Our approach would have been to assess funnel plots visually for asymmetry and if we found asymmetry, we would have performed exploratory analyses to investigate it.

Data synthesis

We conducted meta-analyses if we judged participants, interventions, comparisons and outcomes to be sufficiently similar to ensure an answer that was clinically meaningful. We used the random-effects model with inverse variance weighting for all meta-

analysis, due to anticipated heterogeneity in the study population and outcome measurements. If any trials had multiple treatment groups, we divided the 'shared' comparison group into the number of treatment groups and comparisons between each treatment group and treated the split comparison group as independent comparisons. We performed meta-analysis of the results assuming that included studies were sufficiently similar for the findings to be clinically meaningful.

'Summary of findings' table and results reporting

Based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we prepared 'Summary of findings' (SoF) tables to present the results of the meta-analyses. Where there were sufficient data, we present results for the following outcomes for early (at end of treatment or up to three months or both) and late effects (six months to one year, two to four years, and/or five year time points):

- Mean GI symptom score;
- Moderate or severe GI events (Grade 2+ GI toxicity);
- Moderate or severe diarrhoea (Grade 2+ diarrhoea);
- QoL score.

We used the GRADE system to rate the certainty of the evidence (Schünemann 2011), which was downgraded for inconsistency, design limitations (risk of bias), imprecision, indirectness and other factors, such as publication bias, where appropriate. Where the evidence was based on single studies, or where there was no evidence on a specific outcome, we included the prespecified outcome in the SoF tables and graded or explained accordingly. We downgraded evidence from single studies for imprecision related to small sample size. Two review authors (TL and JG) conducted the grading, resolving differences by discussion and, if necessary, by involving a third review author (MB or Jervoise Andreyev (JA)). Reporting of results in the text was based on the guidance from the Cochrane Effective Practice and Organisation of Care group on review results reporting and interpretation (EPOC 2015).

Subgroup analysis and investigation of heterogeneity

Provided there were sufficient data, we performed subgroup analysis by the type of cancer (urological, gynaecological, and colorectal). This was only practical for comparisons of radiotherapy technique interventions. For other types of interventions, e.g. pharmacological interventions, we subgrouped studies according to the type of drug formulations or the route of administration, where such differences could lead to heterogeneity in the findings. We used formal tests for subgroup differences to determine whether the effect of interventions differed according to these subgroups. If the I^2 for subgroup differences was more than 60%, we considered whether an overall summary was meaningful. We consider factors such as age, gender, type and dose of radiotherapy, previous treatments (abdominal surgery and chemotherapy, or both), and study 'Risk of bias' assessment in interpretation of any heterogeneity. When we identified substantial heterogeneity, we investigated the source using sensitivity analyses.

Sensitivity analysis

We performed some sensitivity analyses by excluding studies at high risk of bias overall, and those at unclear or high risk of bias for specific outcomes (e.g. if we included data on ungraded symptom events). We also performed sensitivity analysis to investigate substantial heterogeneity identified in meta-analyses of primary outcomes.

RESULTS

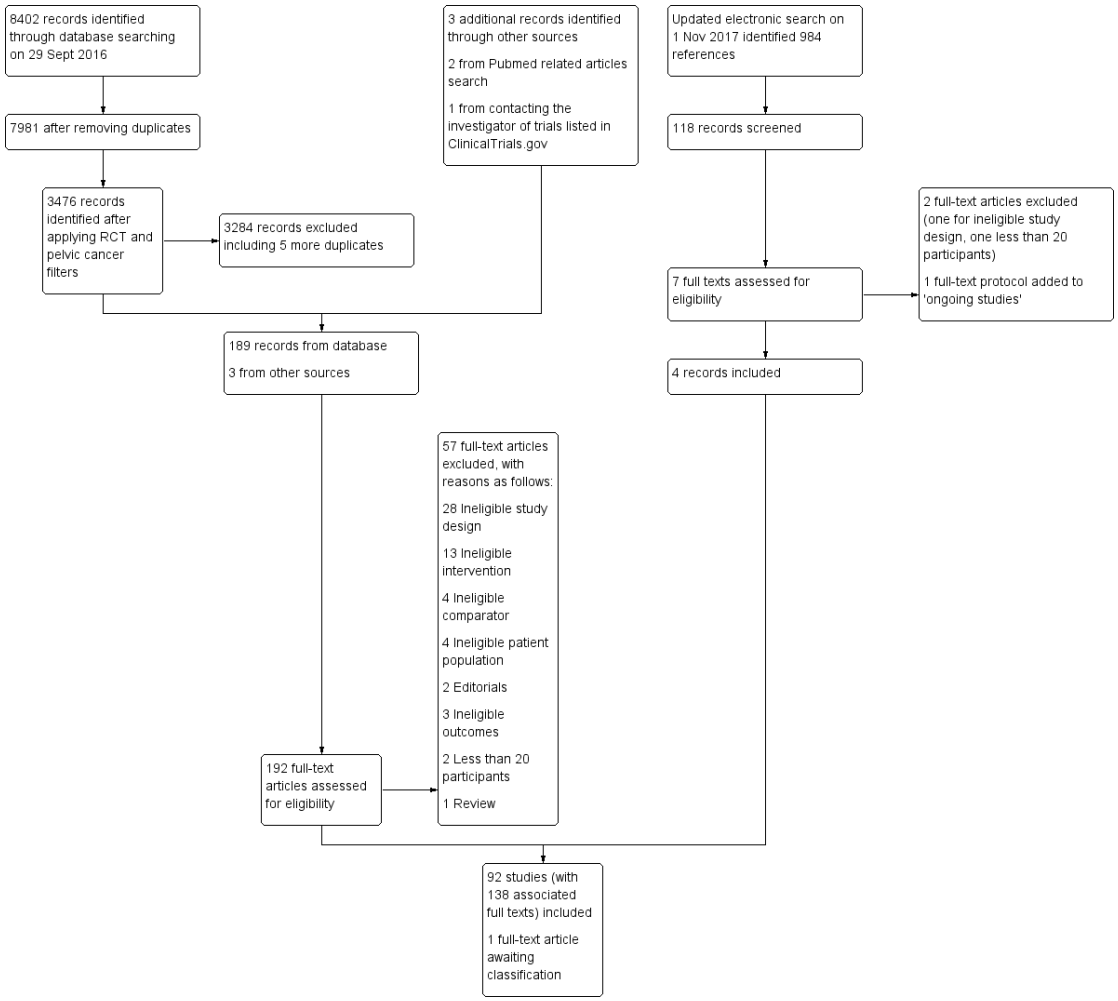
Description of studies

Results of the search

The Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Review Group's Information Specialist ran electronic searches in September 2016 and November 2017.

1. The September 2016 search produced a list of 8402 references. This list was reduced to 7981 by removing duplicates, and then to 3476 references by applying RCT and pelvic cancer filters. Two review authors (TL and JG) independently screened the 3476 references by title and abstract, leading to the identification of 189 references for classification. We found three additional references from other sources (via PubMed and personal communication). Of the total of 192 references identified, we excluded 57 and included 135 references; these were references related to 90 RCTs (Figure 1).

Figure 1. 192Study flow diagram



2. Clinical trial registry searches in September 2016 identified 11 ongoing unpublished trials.
3. The top-up search conducted in November 2017 produced a list of 984 references. Following screening by title and abstract by TL and JG, we obtained the full texts of seven of these references, and examined them for eligibility. Two studies were included, two studies were excluded, one record was added to an already included study, one study was added to Ongoing studies, and one Chinese language article was added to the Studies awaiting classification pending translation.
The review therefore comprises 92 Included studies (involving 138 articles), 59 Excluded studies, 12 Ongoing studies, and one study in Studies awaiting classification.

Included studies

We included 92 RCTs involving 44 different interventions to reduce the GI toxicity of pelvic radiotherapy, and grouped them according to intervention type, namely: radiotherapy techniques, other aspects of radiotherapy delivery, pharmacological interventions, and non-pharmacological interventions. Altogether, more than 10,000 men and women undergoing radiotherapy treatment (primary, adjuvant or neoadjuvant) were randomised to the interventions. GI toxicity was most commonly recorded by investigators according to CTCAE or EORTC RTOG criteria; however, a variety of unvalidated patient questionnaires was also used. More details of the individual studies can be found in the Characteristics of included studies tables. All radiation doses quoted in this review assume a fraction size of 1.8 to 2.0 Gy, unless otherwise stated.

Radiotherapy techniques

This group of 11 studies evaluated four comparisons:

3DCRT versus conventional radiotherapy (conRT)

Three studies randomising approximately 619 participants compared 3DCRT versus conventional radiotherapy (conRT) (Dearnaley 1999; Koper 1999; Tait 1997). Most (79%) of the participants in these studies were men with prostate cancer, except for 128 participants in Tait 1997 with bladder (110), rectal (14) or other (4) cancer. Forty participants (6.5%) in this comparison were women. All participants received RT as primary treatment. Cohorts in Dearnaley 1999 and Tait 1997 overlapped, such that there were an estimated 138 participants common to both studies. Sixty-eight per cent of participants (154/225) in Dearnaley 1999 received hormone treatment, whereas participants in Koper 1999 did not; the proportion of participants receiving hormone treatment was not reported in Tait 1997. The median age of participants reported for Dearnaley 1999 and Tait 1997 ranged from 68 to 72 years (range 50 to 81). Koper 1999 reported similar mean ages for the two study arms (66 and 69 years, respectively). Participants were followed up for at least two years in Dearnaley 1999 and Koper 1999; however, the intended duration of follow-up was unclear in Tait 1997, which only reported early outcomes up to three months post-radiotherapy. Tait 1997 contributed no data to meta-analysis.

IMRT versus conRT

Two studies randomised 94 participants to this comparison (Gandhi 2013; Gudipudi 2014). Participants in both studies were women with cervical cancer who received RT as primary treatment. All participants also received concurrent weekly platinum-based chemotherapy and subsequent vaginal brachytherapy. In Gandhi 2013, the median age of participants was 50 and 45 years for the two study arms (range 35 to 65). Gudipudi 2014 was available only as a conference abstract, with limited methodological, baseline and outcome data. Median duration of follow-up in Gandhi 2013 was approximately 22 months.

IMRT versus 3DCRT

Four studies evaluated this comparison in 447 participants: three studies were conducted in 232 women with cervical cancer (Chopra 2015; Naik 2016; Yu 2015); one was conducted in 215 men with prostate cancer (Viani 2016). Participants in all four studies received RT as primary treatment. Most female participants (94%) additionally received concurrent platinum-based chemotherapy and subsequent vaginal brachytherapy, and 56% of male participants additionally received hormone treatment. The median age of female participants in Naik 2016 and Yu 2015 ranged from 45 to 57, whereas the mean age among men in Viani 2016 was 72 and 71 for each study arm, respectively. Duration of follow-up was 90 days post-radiotherapy for Naik 2016 and three years for Viani 2016 and Yu 2015. Chopra 2015 reported interim results for half of its target sample size in the form of a conference abstract and extractable data were sparse; we understand that follow-up to a median duration of three years is planned (personal communication).

Brachytherapy (BT) versus external beam radiotherapy (EBRT)

Two studies evaluated this comparison. One was a large multicentre study (Nout 2009) involving 427 women with early-stage endometrial cancer; the other was a small study (Manikandan 2015) conducted in 20 men with prostate cancer. In Nout 2009, women with endometrial cancer underwent adjuvant RT following surgery, which consisted of total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), node sampling of suspicious nodes, and peritoneal washings. Vaginal BT delivered as high-dose rate BT of 21 Gy in three fractions of 7 Gy over two weeks (90% of participants) or low-dose rate BT delivered as 30 Gy in one fraction was compared with EBRT of 46 Gy in conventional fractionation. The median age of participants in Nout 2009 was approximately 70 years and participants in this study were followed up for more than seven years. Participants in Manikandan 2015 received RT as primary cancer treatment, in addition to hormone treatment. Both arms of this study received initial treatment of IMRT (45 Gy), and were thereafter randomised to BT or IMRT. At the time of writing, Manikandan 2015 was only available as a conference abstract and extractable data were sparse. This study appears to be ongoing, as a subsequent 2016 conference abstract reported on 30 participants; however, this abstract lacked sufficient detail for data extraction. Furthermore, the target sample size and duration of follow-up are unclear.

Other aspects of radiotherapy delivery

This diverse group of studies comprised 10 different comparisons/interventions evaluated in 14 trials:

Proton versus carbon ion technique

One study (Habl 2016: 92 participants) compared proton ion versus carbon ion techniques in male participants undergoing primary radiotherapy for localised prostate cancer. Twenty-three per cent of participants also received hormone treatment. The radiotherapy dose in both arms of the study was 66 Gy in 20 fractions, alternating between 5 and 6 fractions a week for 3½ weeks. Participants were followed up for 24 months.

Reduced radiation dose volume

Two studies (289 participants: Arafat 2016; Huddart 2013) evaluated the effect of reduced radiation dose volumes compared with standard dose volumes on participants undergoing radiotherapy for bladder cancer. In Arafat 2016, all participants (60) underwent transurethral resection of the bladder tumour (TURBT) before randomisation. Participants in the intervention group received 64 Gy whole bladder radiotherapy alone compared with standard treatment (44 Gy whole pelvis radiotherapy followed by 20 Gy bladder boost). Huddart 2013 (219 participants) was a multicentre study in which centres opted at the outset to use a radiotherapy dose of either 55 Gy/20 fractions over four weeks or 64 Gy/32 fractions over 6½ weeks for all participants. Approximately 90% of participants in Huddart 2013 underwent tumour resection before randomisation. In the standard arm, the planning target volume (PTV) was the outer bladder wall plus the extravesical extent of the tumour with a margin of 1.5 cm. In the experimental arm, two PTVs were defined: PTV1 was the same as for the standard arm, and PTV2 comprised the gross tumour plus a 1.5 cm margin. In this arm, the aim was to deliver 100% of the reference dose to PTV2 and 80% of the reference dose to PTV1. 3DCRT was used. All participants in Arafat 2016 and 30% of participants in Huddart 2013 underwent concurrent chemotherapy. Most participants in these studies (90% and 82%, respectively) were men over the age of 55 years; follow-up was two years in both studies. A third study (Gupta 2009) compared a four-field radiotherapy technique (anterior, posterior and two lateral fields) with a two-field technique (anterior and posterior fields only) in 100 women with cervical cancer. The radiotherapy dose in this study was 40 Gy to whole pelvis, then 10 Gy with midline shield, in conventional fractionation, followed by BT. All participants received radiotherapy as primary treatment. The average age of participants was 48 years and 51 years in four-field and two-field arms, respectively. Participants were followed up for one year.

Belly boards and positioning tables

Two studies evaluated different immobilisation devices (Gaya 2013; Ljubenkovic 2002). Gaya 2013 (30 participants) evaluated a belly board device for RT delivery in the prone position for patients undergoing neoadjuvant chemoradiation for rectal cancer. The radiotherapy dose comprised 45 Gy in 25 fractions over five weeks in both arms, with 5-fluorouracil chemotherapy on weeks 1 and 5 as a radiosensitiser. Ljubenkovic 2002 (183 participants) evaluated a customised positioning table in women with cervical cancer. Comparator arms were standard radiotherapy protocols in both studies. The median age of participants was 64 years in Gaya 2013. This study reported mainly dosimetric parameters and both studies had little to no usable review data; findings are therefore briefly described in Table 2.

Evening radiotherapy treatment

Two studies (Shukla 2010; Chang 2016) evaluated evening radiotherapy delivery compared with morning radiotherapy delivery in 229 women and 67 women, respectively, receiving primary RT for cervical cancer. Mean participant age in these studies ranged from 47 to 50 years in the study arms, and both groups also received intracavitatory brachytherapy. Follow-up in these studies was limited to the period of RT.

Bladder volume preparation

Mullaney 2014 compared pre-RT bladder-filling protocols of 1080 ml compared with 540 ml in 110 men receiving primary RT for prostate cancer. The policy at the institution in which the study was conducted was to instruct patients to empty their bladder, drink 1080 ml of water and wait 30 to 40 minutes prior to undergoing RT.

Hyperbaric oxygen

Sidik 2007 compared hyperbaric oxygen therapy (HBOT) with no HBOT in 65 women undergoing primary RT for cervical cancer. This study reported scant data on review outcomes, and findings are summarised in Table 2.

Prerectal spacers

Two studies evaluated a transperitoneal hydrogel spacer/injection (Mariados 2015; Prada 2009) compared with no spacer in 229 and 69 men undergoing RT for prostate cancer, respectively. The mean age across study groups ranged from 66 to 69 years. The RT technique employed in Mariados 2015 was IG-IMRT (79.2 Gy in 1.8-Gy fractions) and in Prada 2009 was BT, with the duration of follow-up in Mariados 2015 of up to 15 months in the main report, and in Prada 2009 a median of 26 months. A follow-up study of Mariados 2015 (Hamstra 2017) involved 63% of the original sample at a median of approximately three years post-enrolment.

Endorectal balloons (ERBs)

Two studies evaluated ERBs in men undergoing primary RT for prostate cancer (Botten 2015; Van Lin 2007). Botten 2015 at the time of writing has only been reported as conference abstracts with little usable data. Mean age of the men in this study was 72 years but other details are scant, including the RT regimen used. In Van Lin 2007 (48 participants), participant characteristics are lacking in the report, but the RT regimen described was 67.5 Gy delivered in 7½ weeks (four fractions a week) in 2.25-Gy daily fractions. Participants were followed up for 30 months in Van Lin 2007 and for one year in Botten 2015.

Pharmacological interventions

This group of studies comprised 16 different interventions evaluated in 38 trials:

Anti-inflammatory agents

Aminosalicylates

Seven studies (583 participants) evaluated different formulations of aminosalicylates (5-ASAs) including balsalazide (Jahraus 2005; 27 participants), sulfasalazine (Kilic 2000; Miller 2016; Pal 2013; 272 participants altogether), olsalazine (Martenson 1996; 58 participants) and mesalazine (Resbeut 1997; 153 participants; Baughan 1993; 73 participants). Jahraus 2005 and Pal 2013 exclusively enrolled men with prostate cancer and women with cervical cancer, respectively. The other studies enrolled both men and women with pelvic cancer in whom mostly primary radiotherapy treatment was indicated. Radiotherapy doses ranged from 30 Gy to 60 Gy in conventional fractionation over three to seven weeks. Overall, women comprised 23% (137/583) of participants enrolled in all seven studies. Aminosalicylates versus placebo were administered orally in all studies. The dose of sulfasalazine in three studies was 1000 mg twice daily (Kilic 2000; Miller 2016; Pal 2013); the dose of balsalzide was 2250 g twice daily (Jahraus 2005); the dose of olsalazine was 500 mg twice daily (Martenson 1996); the equivalent dose of 5-ASA was 2000 mg twice daily in Resbeut 1997 and 800 mg three times daily in Baughan 1993. The intervention began at the start of radiotherapy and was continued daily throughout radiotherapy treatment. In five studies, the intervention continued after radiotherapy for a variable period of one to four weeks. The longest follow-up among this group of studies was three months (Resbeut 1997). The olsalazine study (Martenson 1996) closed early as more participants in the experimental arm suffered severe toxicity (diarrhoea grade 3) attributed to the study medication.

One other three-arm study (Sanguineti 2003) compared a hydrocortisone 100 mg foam enema with sucralfate 3 g suspension enema and mesalazine 4 g gel enema in 134 men undergoing primary radiotherapy at a dose of 76 Gy in conventional fractionation; however, the mesalazine arm was discontinued early in the study, following an unplanned interim analysis that indicated drug-related toxicity with mesalazine in seven out of the eight participants recruited to this study arm.

Ibuprofen

One study (Stryker 1979) evaluated oral ibuprofen (400 mg six-hourly) compared with no intervention in 32 participants (31 with gynaecological cancer and one with prostate cancer) undergoing primary radiotherapy. The mean age of participants was 60 years and 56 years for study and control groups, respectively. The intervention began at the start of radiotherapy and continued for the duration (five to six weeks) of radiation treatment. Participants were followed up during radiotherapy only (See Table 2).

Corticosteroids

Two studies (Fuccio 2011; Sanguineti 2003) evaluated corticosteroid enemas in men undergoing radiotherapy for prostate cancer. Fuccio 2011 evaluated rectal beclomethasone dipropionate versus placebo in 120 men with a mean age of approximately 70 years. Just over half of these participants had undergone primary surgery (prostatectomy), with 30% receiving hormone therapy. The radiotherapy dose ranged from 66 to 74 Gy in conventional fractionation. The intervention was administered as a 3 mg enema during the radiotherapy treatment period and as a twice-daily 3 mg suppository for four weeks after radiotherapy. Participants were followed up for 12 months and the study reported cumulative incidence of GI toxicity up to 12 months. Sanguineti 2003 was a three-arm study that compared a hydrocortisone 100 mg foam enema with sucralfate 3 g suspension enema and mesalazine 4 g gel enema in 134 men undergoing primary radiotherapy for prostate cancer at a dose of 76 Gy in conventional fractionation. The mean/median age of participants was not reported. The mesalazine arm was discontinued early in the study following an unplanned interim analysis that indicated drug-related toxicity with mesalazine. The investigators chose to compare hydrocortisone to sucralfate "because it (sucralfate) had not shown any benefit over placebo in a previous double-blind randomised study".

Orgotein (superoxide dismutase)

Two studies evaluated this agent in participants undergoing radiotherapy for rectal (Esco 2004) and bladder cancer (Menander-Huber 1978). Participants in Esco 2004 received adjuvant radiotherapy at a dose of 50 Gy in conventional fractionation, and in Menander-Huber 1978 received primary radiotherapy treatment using an outdated technique. Orgotein was administered by subcutaneous (SC) and intramuscular (IM) injection in these studies, respectively. In Esco 2004, IM injections were given three times weekly during treatment and, in Menander-Huber 1978, SC injections were administered after each daily radiotherapy fraction. Participants were followed up for two years in both studies.

Amifostine

Five studies evaluated amifostine administered before radiotherapy; four compared subcutaneously (SC) (Katsanos 2010; Koukourakis 2000) or intravenously (IV) (Athanassiou 2003; Kouvaris 2003) administered amifostine versus no intervention, and one compared SC amifostine (500mg) with a 1500 mg amifostine enema (Kouloulias 2005). Amifostine regimens were usually a 500 mg single dose daily before RT, except for Athanassiou 2003, which administered an IV dose of 340 mg/m^2. Participants in four of the studies were men and women undergoing primary

or adjuvant radiotherapy for pelvic cancers; however, one study (Koukourakis 2000) included a subgroup of participants with pelvic cancer (40 out of 140 male and female participants) and reported outcomes separately by subgroup. Radiotherapy doses ranged from 44 Gy to 72 Gy in conventional fractionation in these studies, depending on the type of cancer. Follow-up reportedly ranged from six to 12 months post-radiotherapy in these studies; however, most studies reported acute effects only.

Bile acid sequestrants

Two small older studies evaluated these agents (Chary 1984; Stryker 1983). Chary 1984 compared cholestyramine with placebo during and for two months after radiotherapy; Stryker 1983 compared colestipol with no intervention during radiotherapy treatment only. Both involved a mixed group of participants with pelvic cancers; Chary 1984 involved mainly male participants (23/33; 70%) whereas Stryker 1983 involved mainly female participants (28/31; 89%). Most participants (27/33) in Chary 1984 were undergoing primary radiotherapy, whereas most (25/31) in Stryker 1983 were undergoing adjuvant radiotherapy. A radiotherapy dose of 50 Gy in standard fractions over five days for a period of five to six weeks was delivered to participants in Chary 1984, and 'standard whole pelvic radiation' was given to participants in Stryker 1983. The mean age of participants was approximately 68 years in Chary 1984 and 57 years in Stryker 1983. Follow-up in Chary 1984 was up to two months post-radiotherapy and for Stryker 1983 was during treatment only.

Famotidine

One pilot study (Razzaghdoust 2014) randomised 36 men with prostate cancer to the H2 receptor antagonist famotidine (40 mg orally before each radiotherapy fraction) or placebo. Primary radiotherapy treatment comprised a dose of 70 Gy in conventional fractions. Participants also received hormone treatment. The mean age of participants was approximately 68 years and 66 years in the intervention and placebo arms, respectively. Participants were followed up during radiotherapy only.

Magnesium oxide

One study (Lips 2011: 92 participants) evaluated oral magnesium oxide (500 mg twice daily) versus placebo in men undergoing primary radiotherapy (77 Gy in 35 fractions) for prostate cancer. The median age of participants was approximately 71 years and approximately half of participants also received hormonal treatment. Follow-up was conducted up to four weeks post-radiotherapy.

Misoprostol

One study (Hille 2005) evaluated the effects of misoprostol rectal suppositories (400 µg) versus placebo in 100 men undergoing primary radiotherapy treatment for prostate cancer. The radiotherapy dose ranged from 45 Gy to 72 Gy in standard fractionation and boost delivered using the 3DCRT technique. Most participants (82%) also received concurrent hormone therapy. Suppositories were administered one hour before each radiotherapy fraction. Mean age of participants was approximately 68 years. Participants were followed up for a median of 50 months.

Octreotide

Two studies (363 participants) compared long-acting octreotide acetate with placebo in patients undergoing radiotherapy for pelvic (Martenson 2008) and anorectal cancer (Zachariah 2010), respectively. Martenson 2008 included participants with rectal (45/125; 36%), prostate (38/125; 30%), gynaecological (36/125; 29%) and other (6/125; 5%) cancers. Sixty-one per cent of participants in Martenson 2008 and 82% of those in Zachariah 2010 also received concurrent chemotherapy. Octreotide was delivered as 100 µg SC test dose on Day 1 of radiotherapy, followed by 20 mg intramuscularly (IM) on Day 2 (if tolerant) and Day 29 in Martenson 2008; in Zachariah 2010 a dose of 30 mg was given IM four to seven days before the start of radiotherapy and again on Day 22 of radiotherapy treatment. The planned radiotherapy dose was 45 Gy in conventional fractionation for both studies; however, the proportion of participants receiving adjuvant and primary radiotherapy was not stated. Women comprised 37% of the sample in Zachariah 2010, and the gender of participants in Martenson 2008 was not stated. Follow-up in Martenson 2008 occurred during radiotherapy only, whereas in Zachariah 2010 follow-up was conducted for 15 months post-radiotherapy.

Selenium

One study (Muecke 2010: 81 participants) evaluated the effects of oral selenium supplements (500 mg on the days of radiotherapy and 300 mg on the rest days) compared with no intervention in women undergoing adjuvant radiotherapy for gynaecological cancers. External radiotherapy was delivered in conventional fractionation, with optional brachytherapy according to German guidelines. Median age of participants in the intervention and control groups was 64.8 years and 63.8 years, respectively. Participants were followed up for six weeks after radiotherapy.

Simethicone

This agent was evaluated in one study (McGuffin 2016) conducted among 78 participants undergoing primary radiotherapy for prostate cancer. At the time of writing, the report was available as a conference abstract only.

Smectite

One study (Hombrink 2000: 176 participants) evaluated oral smectite (6 g twice daily) compared with placebo in a mixed population undergoing radiotherapy for mainly pelvic cancers.

Sodium butyrate

One study (Maggio 2014: 166 participants) evaluated this agent in men undergoing radiotherapy for prostate cancer. Sodium butyrate was administered as an enema in different doses (1 g, 2 g and 4 g) to three study arms and compared with a placebo arm. Half the total sodium butyrate dose in the intervention arm was administered after radiotherapy and the other half was administered eight to 12 hours later. Radiotherapy was indicated as primary treatment and the radiotherapy dose was 70 Gy in conventional fractionation using a 3DCRT technique; 61% of participants also received hormone therapy. The mean age of participants was not stated. Participants were followed up for six weeks post-radiotherapy.

Sucralfate

Sucralfate was evaluated in 10 studies (1115 participants) altogether, either as an oral (Henriksson 1990; Henriksson 1991; Hovdenak 2005; Kneebone 2001; Martenson 2000; Stellermans 2002; Valls 1991; Valls 1999) or rectal preparation (O'Brien 1997; Sanguineti 2003). Three of the studies were conducted in men undergoing primary radiotherapy for prostate cancer (Kneebone 2001; O'Brien 1997; Sanguineti 2003), one was conducted in women requiring adjuvant radiotherapy for gynaecological cancers (Henriksson 1990), and the rest were conducted in a mixed population undergoing primary radiotherapy for various pelvic cancers. Women comprised 25.7% (219/851) of the seven studies that reported participant gender; three studies (Hovdenak 2005; Henriksson 1991; Stellermans 2002) with 70, 52 and 108 participants respectively did not report gender characteristics of their samples. Oral doses ranged from 4 g to 8 g a day in three or four divided doses. Enemas consisted of a 3 g sucralfate dose given daily before radiotherapy fractions. Interventions were compared with placebos in all studies except for Henriksson 1990 (which compared sucralfate with no treatment) and Sanguineti 2003 (which compared sucralfate with mesalazine or hydrocortisone). In the latter study, the mesalazine arm was discontinued due to toxicity. Standard radiotherapy doses and fractionation were used in these studies. Follow-up was fairly short-term in most of the studies, but four studies followed up participants for a year or more.

Tropisetron

One three-arm study (Kardamakis 1995: 33 participants) evaluated this serotonin 5-HT_3 receptor antagonist (25 mg daily tropisetron orally) given for six or three weeks from the start of radiotherapy treatment versus placebo in a mixed patient population undergoing primary radiotherapy for various pelvic cancers. This study was reported briefly in letter format and contained little study information or extractable data.

Non-pharmacological interventions

This group of studies comprised 13 interventions evaluated in 29 trials.

Probiotics

Eight studies (983 participants) evaluated probiotic preparations that included lactobacilli, with or without bifidobacteria and other probiotic strains (Chitapanarux 2010; Delia 2007; Demers 2014; Giralt 2008; Nascimento 2014; Mansouri-Tehrani 2016; Salminen 1988; Timko 2010). Nascimento 2014 and Salminen 1988 combined the probiotic intervention with a prebiotic diet (synbiotic interventions). Mansouri-Tehrani 2016 compared a probiotic preparation administered with or without honey to placebo in a three-arm study. Doses and strains of probiotics varied widely across the studies. Three of the studies were conducted in women with gynaecological cancers (Chitapanarux 2010; Giralt 2008; Salminen 1988), in which radiotherapy was the primary treatment in Chitapanarux 2010, and was primary or adjuvant treatment in Giralt 2008 and Salminen 1988. One small study was conducted in men undergoing primary radiotherapy for prostate cancer (Nascimento 2014), and the other four were conducted in men and women undergoing primary or adjuvant radiotherapy for various pelvic cancers. One large study (Delia 2007) did not report baseline characteristics of the participants. Of the other seven studies, women comprised 60% (300/501) of the participants evaluated, with the mean or median age reported for each study group ranging from 47 to 70 years. Follow-up of participants in most studies was limited to the period of radiotherapy treatment and a few weeks thereafter; however, one study (Timko 2010) followed up participants for six months after radiotherapy.

Nutritional interventions

Studies evaluated various types of nutritional interventions including:

Elemental diet

One small study (McGough 2008: 50 participants) evaluated the effect of an elemental diet versus a regular diet in participants undergoing primary or adjuvant radiotherapy for various pelvic cancers. The sample comprised 28 women and 22 men. Mean radiotherapy dose ranged from 50.4 Gy to 54 Gy in conventional fractionation. Some participants also received concomitant chemotherapy. Participants in the elemental intervention group were asked to replace one meal a day, equivalent to 33% of total caloric

requirements, with elemental diet (E028) with calories from fat sources comprising 35% of formula provided in the form of ready-to-drink 250 mL cartons and powder sachets. Overall compliance was only 21% of replacement of total caloric requirement. Participants were followed up for 10 weeks.

Lactose-restricted diet

One small three-arm study (Stryker 1986: 64 participants) evaluated a lactose-restricted diet versus a modified lactose or regular diet in participants undergoing primary or adjuvant radiotherapy for various pelvic cancers. Most participants (89%) were women with gynaecological cancers. Standard radiotherapy doses and fractions were used. Follow-up occurred during the period of radiotherapy only.

Fibre-modified diets

Four studies (318 participants) evaluated fibre-modified diets compared with regular diets, including Garcia-Peris 2016 (6 g mixed fibre twice daily from one week before radiotherapy to three weeks after versus placebo); Itoh 2015 (1 g hydrolyzed rice bran three times a day versus placebo); Murphy 2000 (psyllium agent versus no intervention); and Wedlake 2017 (high-fibre (> 18 g per day) versus low-fibre (< 10 g per day) versus regular diet). Participants in Itoh 2015 (20 participants) and Wedlake 2017 (166 participants) were undergoing primary radiotherapy treatment for various pelvic cancers, those in Garcia-Peris 2016 (48 participants) were undergoing adjuvant radiotherapy for gynaecological cancers, and the type of radiotherapy treatment (primary or adjuvant) was not stated in Murphy 2000 (84 participants). All participants in Itoh 2015 and 72% of participants in Wedlake 2017 received concomitant chemotherapy. Women comprised all participants in Itoh 2015 and Garcia-Peris 2016, and 58% and 15% of participants in Wedlake 2017 and Murphy 2000, respectively. Follow-up in these studies was limited to the radiotherapy period only in Itoh 2015, and to three months (Garcia-Peris 2016), six months (Murphy 2000) or one year (Wedlake 2017) post-radiotherapy in the other studies.

Low-fat diets

One three-arm study (Wedlake 2012: 117 participants) evaluated a low-fat (less than 20% of dietary energy from fat) versus a modified-fat (40% of dietary energy from fat, with 50% to be derived from a liquid supplement) versus a normal-fat diet (40% of dietary energy from fat). Participants included a mixed population undergoing primary radiotherapy (54 Gy to 64 Gy in conventional fractionation) for various pelvic cancers; 50% of participants also received concomitant chemotherapy. Approximate two-thirds of participants were men. Follow-up was conducted up to one year post-radiotherapy.

Prebiotic diet

The one study included in this group was also included in the fibre-modified diet comparison above as the intervention (inulin and fructo-oligosaccharide added to restrictive diet) could be classed as both or either. Participants in Garcia-Peris 2016 (48 participants) were women undergoing adjuvant radiotherapy for gynaecological cancers, as described above.

'Steady' diet

One small study (Arregui Lopez 2012: 29 participants) evaluated a 'steady diet' versus a 'diet based on general recommendations'. At the time of writing, the report of this Spanish study was available as a conference abstract only and it was not clear what was meant by a 'steady' diet. We included this study anticipating that the full report would contain details of the dietary intervention. Participants in this study were undergoing adjuvant radiotherapy (median dose of 45 Gy) for rectal cancer and they also appear to have received neoadjuvant chemotherapy. Follow-up was conducted up to three weeks post-radiotherapy.

Soy diet

One small study (Ahmad 2010: 42 participants) evaluated a 'soy diet' versus a regular diet among male participants undergoing primary radiotherapy for prostate cancer. The intervention (100 mg tablet of soy isoflavones twice daily), which began on the first day of radiation and continued for six months, was compared with placebo. The radiotherapy dose, ranging from 73.8 Gy to 77.5 Gy, was delivered in conventional fractionation. No participants received chemotherapy or hormone therapy. Median ages of participants were 60 and 65 years for intervention and placebo groups, respectively. Attrition was high in this study, which aimed to follow up participants for six months.

High-protein supplements

One three-arm study (Ravasco 2005) compared a high-protein supplement in addition to the usual diet, with usual diet or an individualised dietary counselling intervention among 111 participants (60% male) undergoing primary or adjuvant radiotherapy for colorectal cancer. The protein supplement was a commercial product available in a 200 ml can providing 20 g protein and 200 kcal; participants in the protein supplement arm received two cans a day. Radiotherapy consisted of 50.4 Gy in conventional fractionation, with an initial study follow-up of three months (Also see 'Counselling' interventions below).

Glutamine

Five studies (358 participants) evaluated the effects of oral glutamine (Kozelsky 2003; Manir 2014; Rotovnik Kozjek 2011;

Vidal-Casariego 2014) or glutathione (De Maria 1992) versus placebo in people undergoing primary or adjuvant radiotherapy for pelvic cancer. Participants in these studies included both men and women, except for De Maria 1992 which included only women with endometrial cancer. Overall, women comprised 48% of all participants and the mean or median age across study groups ranged from 57 years to 67.5 years. The radiotherapy doses used in these studies ranged from 45 Gy to 60 Gy in conventional fractionation. Most studies evaluated outcomes during radiotherapy only. One study (Kozelsky 2003) apparently followed up participants for two years but contributed very little long-term data.

Other non-pharmacological interventions

Counselling

Two studies evaluated counselling interventions: Kim 2002 evaluated a counselling intervention on what to expect with radiotherapy treatment among 184 male participants undergoing primary radiotherapy for prostate cancer; Ravasco 2005 evaluated a dietary counselling intervention among 111 participants (60% male) undergoing primary or adjuvant radiotherapy for colorectal cancer. In this study, individualised dietary counselling based on a person's regular diet was compared with a high-protein supplement in addition to a regular diet, or a regular diet only. Participants in the dietary counselling arm received a prescription diet using regular foods and adjusted to the individual's usual diet, "thereby recognizing personal eating patterns and preferences". The dose of radiotherapy in Ravasco 2005 was 50.4 Gy in conventional fractionation but was not stated in Kim 2002. Duration of follow-up in Ravasco 2005 was three months initially, but a subsequent report included follow-up at a median of 6½ months. Follow-up in Kim 2002 was conducted during radiotherapy treatment only.

Curcumin

A pilot study (Hejazi 2013) of 45 participants (40 analysed) evaluated curcumin (turmeric) tablets versus placebo in men undergoing radiotherapy for prostate cancer. Curcumin tablets (1 g three times a day with meals) or placebo tablets were started one week before radiotherapy and continued throughout the treatment period. The radiotherapy dose was 74 Gy in conventional fractionation. Participants with a mean age of 69.7 years and 71.9 years in intervention and placebo arms, respectively, were followed up for three months after radiotherapy.

Green tea

One small study (Emami 2014: 42 participants) evaluated green tea tablets versus placebo in a mixed population undergoing primary or adjuvant radiotherapy for various pelvic cancers. The dose of green tea was 450 mg daily for five weeks (duration of radiotherapy treatment). Forty-five per cent of evaluated participants were women and the mean age in the green tea and placebo groups was 65.7 years and 58.7 years, respectively. The radiotherapy dose was 50 Gy in conventional fractionation. Follow-up occurred for four weeks post-radiotherapy.

Proteolytic enzymes

Two studies (176 participants) evaluated capsules containing papain, trypsin and chymotrypsin enzymes (Dale 2001; Martin 2002); Dale 2001 compared the enzymes with no intervention and Martin 2002 compared the enzymes with placebo. Participants in Dale 2001 (120 women) were undergoing primary radiotherapy (50 Gy to 60 Gy in conventional fractionation, plus brachytherapy) for cervical cancer. Participants in Martin 2002 (56 participants) were women (73%) and men (27%) undergoing adjuvant radiotherapy (50.4 Gy in conventional fractionation) for various pelvic cancers. Mean age of participants in Dale 2001 was 49.9 years in the intervention group and 49.3 years in the control group, and for Martin 2002 were 53.8 years and 57.3 years, respectively. Dale 2001 followed participants up for three months after radiotherapy, whereas follow-up in Martin 2002 occurred during radiotherapy treatment only.

Excluded studies

Fifty-nine studies were excluded (57 from September 2016 and two from the November 2017 full texts assessed) for the following reasons:

- Ineligible study design, e.g. observational study (29 studies)
- Ineligible intervention, e.g. dose escalation study (13 studies)
- Ineligible comparator, e.g. chemotherapy (4 studies)
- Ineligible patient population, e.g. people with non-pelvic cancers (4 studies)
- Ineligible outcomes, e.g. dosimetric parameters only (3 studies)
- Published editorial or review (3 publications)
- Fewer than 20 participants (3 studies)

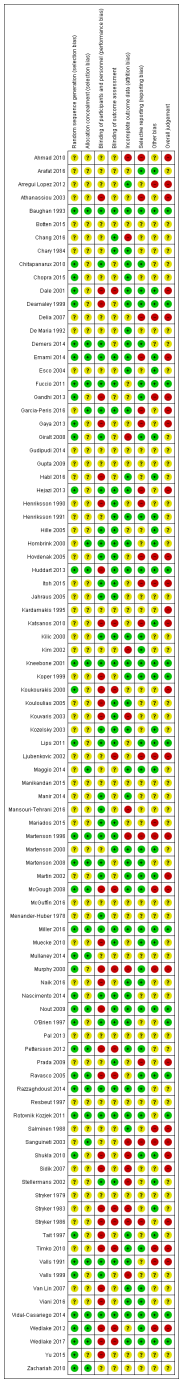
For a complete list of excluded studies with reasons, please refer to the Characteristics of excluded studies section.
Also see Potential biases in the review process where we discuss some of the more difficult decisions taken.

Risk of bias in included studies

Overall 'Risk of bias' judgements are reported below. For individual judgements for each of the 'Risk of bias' domains for each

included study that informed the overall 'Risk of bias' judgement, please refer to the 'Risk of bias' tables in the Characteristics of included studies section and Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Studies of radiotherapy techniques (11 studies)

We judged the risk of bias of three of these RCTs as low risk (Dearnaley 1999; Koper 1999; Nout 2009), seven as unclear risk (Chopra 2015; Gudipudi 2014; Manikandan 2015; Naik 2016; Tait 1997; Viani 2016; Yu 2015) and one as high risk overall (Gandhi 2013). We assigned an overall assessment of unclear risk when study methods had not been described in sufficient detail to make a judgement in several domains, in the absence of serious risk of bias concerns for any specific domain (apart from blinding). Two of these study reports were conference abstracts (Gudipudi 2014; Manikandan 2015), with scant methodological information and outcome data. We rated Gandhi 2013 at high risk of bias potential as this trial did not have a prespecified and adequately-powered sample size and its positive findings could have influenced the decision to stop the trial.

Studies of other aspects of radiotherapy delivery (14 studies)

We judged most of these studies as having an unclear risk of bias overall, due to insufficient information on study methods or due to methodological limitations. However, we rated the two studies evaluating belly boards or positioning devices (Gaya 2013; Ljubenkovic 2002), the study evaluating a transperineal hyaluronic acid injection (Prada 2009) and the study on hyperbaric oxygen (Sidik 2007) at high risk of bias. Huddart 2013, evaluating a reduced radiation dose volume intervention, was the only study assessed as having a low risk of bias overall.

Studies of pharmacological interventions (38 studies)

Aminosalicylates: We rated the seven aminosalicylate studies at low (Baughan 1993; Jahraus 2005; Miller 2016) or unclear risk of bias overall (Kilic 2000; Pal 2013; Martenson 2000; Resbeut 1997). Methodology was poorly described in Kilic 2000; Pal 2013; Martenson 2000 and Resbeut 1997, making judgement of overall risk of bias impossible.

Amifostine: We judged these five studies either as high risk of bias overall (Athanassiou 2003; Katsanos 2010; Kouloulias 2005) or unclear risk (Koukourakis 2000; Kouvaris 2003), mainly due to methodological or reporting limitations, or both.

Sucralfate: We rated these 10 studies at low (Kneebone 2001), unclear (Henriksson 1990; Henriksson 1991; Martenson 2000; O'Brien 1997; Sanguineti 2003; Stellermans 2002; Valls 1991; Valls 1999) or high risk of bias (Hovdenak 2005). In addition to lacking details on randomisation and allocation methods in the report, the high risk of bias study was stopped early following an unplanned interim analysis of 44 evaluable participants that showed significantly increased diarrhoea in the sucralfate group. Studies judged to be at unclear risk of bias mostly lacked methodological details in their reports or there were inconsistencies that cast some doubt on the findings (e.g. Henriksson 1990) or the baseline characteristics of the participants were imbalanced (e.g. Valls 1991, which included seven participants with colostomies in the intervention arm and three in the control arm).

Corticosteroids: We rated Fuccio 2011 at low risk of bias and Sanguineti 2003 at unclear risk of bias overall.

Octreotide: We judged Martenson 2008 as having unclear risk of bias overall, due to imbalances in baseline characteristics between intervention and placebo groups. We rated Zachariah 2010 at unclear risk of bias, as the report lacked certain methodological details on which we could base risk of bias judgements.

Other pharmacological interventions: The methodology of most of these studies was poorly described in the available reports and led to judgements of unclear risk of bias overall (bile acid sequestrants: Chary 1984; Stryker 1983; ibuprofen: Stryker 1979; misoprostol: Hille 2005; orgotein: Esco 2004; Menander-Huber 1978; selenium: Muecke 2010; simethcone: McGuffin 2016; smectite: Hombrink 2000; sodium butyrate: Maggio 2014; tropisetron: Kardamakis 1995). We judged two studies (famotidine: Razzaghdoust 2014; magnesium oxide: Lips 2011) as having low risk of bias overall.

Non-pharmacological interventions (29 studies)

Dietary interventions: We rated most RCTs at high risk of bias overall (Ahmad 2010; Arregui Lopez 2012; Garcia-Peris 2016; Itoh 2015; McGough 2008; Murphy 2000; Stryker 1986; Wedlake 2012). We judged one individual RCT as being at low risk of bias overall (Wedlake 2017; fibre diet) and one at unclear risk of bias (Pettersson 2012).

Probiotics: We rated most of these studies at unclear risk of bias (Chitapanarux 2010; Demers 2014; Giralt 2008; Nascimento 2014; Mansouri-Tehrani 2016; Salminen 1988; Timko 2010), and high risk of bias overall (Delia 2007).

Glutamine: We judged two studies to have a low risk of bias overall (Rotovnik Kozjek 2011; Vidal-Casariego 2014) and three studies to have an unclear risk of bias overall (De Maria 1992; Kozelsky 2003; Manir 2014).

Counselling: We judged Ravasco 2005 (dietary counselling) to be at low risk of bias overall, whereas Kim 2002 (counselling on what to expect with RT) was at unclear risk of bias.

Protein supplements: See Ravasco 2005 above (counselling).

Other interventions: We rated the two studies of proteolytic en-

zymes to be at high risk of bias overall (Dale 2001; Martin 2002), and Emami 2014 (green tea) and Hejazi 2013 (curcumin) to be at unclear and high risks of bias, respectively.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: Conformal RT vs conventional RT; **Summary of findings 2** Summary of findings: IMRT vs 3DCRT; **Summary of findings 3** Summary of findings: BT vs EBRT; **Summary of findings 4** Summary of findings: Reduced dose volume vs standard dose volume; **Summary of findings 5** Summary of findings: Higher bladder volume vs lower bladder volume; **Summary of findings 6** Summary of findings: Evening RT vs morning RT; **Summary of findings 7** Summary of findings: Hydrogel spacer vs no intervention; **Summary of findings 8** Summary of findings: Endorectal balloon vs no intervention; **Summary of findings 9** Summary of findings: Aminosalicylates vs placebo; **Summary of findings 10** Summary of findings: Superoxide dismutase vs no intervention; **Summary of findings 11** Summary of findings: Corticosteroids vs placebo; **Summary of findings 12** Summary of findings: Sucralfate vs placebo; **Summary of findings 13** Summary of findings: Amifostine vs no intervention; **Summary of findings 14** Summary of findings: Sodium butyrate vs placebo; **Summary of findings 15** Summary of findings: Selenium vs no intervention; **Summary of findings 16** Summary of findings: Bile acid sequestrants vs no intervention; **Summary of findings 17** Summary of findings: Misoprostol vs placebo; **Summary of findings 18** Summary of findings: Magnesium oxide vs placebo; **Summary of findings 19** Summary of findings: Octreotide vs placebo; **Summary of findings 20** Summary of findings: Diet interventions vs usual on-treatment diet; **Summary of findings 21** Summary of findings: Protein supplements vs no intervention; **Summary of findings 22** Summary of findings: Probiotics vs control (placebo or no intervention); **Summary of findings 23** Summary of findings: Proteolytic enzymes vs control (placebo or no intervention); **Summary of findings 24** Summary of findings: Glutamine vs placebo; **Summary of findings 25** Summary of findings: Counselling vs no intervention

We summarise the findings of certain interventions that have been evaluated in only a single small (underpowered) study or in a study with no usable data on review outcomes in Table 2.

Radiotherapy techniques

Conformal RT (3DCRT and/or IMRT) compared with conventional radiotherapy (conRT)

Study participants in the 3DCRT subgroup (n = 473) were mostly men with prostate cancer and those in the IMRT subgroup (n = 44) were women with cervical cancer.

- *GI symptom scores:* No evidence was found.
- *GI toxicity (grade 2+):* High-certainty evidence shows that conformal RT is associated with less acute GI toxicity (grade 2+) than conventional RT (risk ratio (RR) 0.57, 95% confidence interval (CI) 0.40 to 0.82; participants = 307; studies = 2; I^2 = 0%; Analysis 1.1); however, moderate-certainty evidence suggests that there is probably little or no difference in late GI toxicity grade 2+ (RR 0.49, 95% CI 0.22 to 1.09; participants = 517; studies = 3; I^2 = 44%; Analysis 1.2). Subgroup findings for these outcomes were consistent with the pooled estimates. When the grade 1 events are included in the analysis, low-certainty evidence suggests that there may be little or no difference between conformal and conventional RT with regard to acute grade 1+ GI toxicity (RR 0.75, 95% CI 0.42 to 1.36; participants = 307; studies = 2; I^2 = 68%; Analysis 1.3) and late grade 1+ GI toxicity (RR 0.55, 95% CI 0.19 to 1.59; participants = 292; studies = 2; I^2 = 72%; Analysis 1.4).
- *Diarrhoea (grade 2+):* No evidence was found.
- *Other GI symptoms (grade 2+)*: Evidence on vomiting is of a very low certainty (Analysis 1.5) and we found no evidence on other GI symptoms.
- *Medication use for GI symptom control:* Moderate-certainty evidence suggests that there is probably little or no difference in the use of medication for symptom control (RR 0.86, 95% CI 0.44 to 1.66; participants = 263; studies = 1; Analysis 1.6).
- *Other review outcomes*: There were no data for meta-analysis on QoL or other review outcomes.

IMRT compared with 3DCRT

- *GI symptom scores:* Low-certainty evidence suggests that GI symptom scores on the EORTC QLQ25 scale may be better with IMRT at various time points, including six months (mean difference (MD) -5.00, 95% CI -9.06 to -0.94; participants = 181; studies = 1; Analysis 2.1) and two years (MD -7.00, 95% CI -13.45 to -0.55; participants = 165; studies = 1; Analysis 2.2).
- *GI toxicity (grade 2+):* Low-certainty evidence suggests that IMRT may be associated with less acute GI toxicity grade 2+ than 3DCRT (RR 0.48, 95% CI 0.26 to 0.88; participants = 444; studies = 4; I^2 = 77%; Analysis 2.3) and less late GI toxicity grade 2+ (RR 0.37, 95% CI 0.21 to 0.65; participants = 332; studies = 2; I^2 = 0%; Analysis 2.4). Including grade 1 GI toxicity data, the evidence suggesting a benefit with IMRT remains low certainty for acute toxicity grade 1+ (RR 0.59, 95% CI 0.41 to 0.86; participants = 444; studies = 4; I^2 = 69%; Analysis 2.5) and late grade 1+ toxicity (RR 0.65, 95% CI 0.46 to 0.93; participants = 332; studies = 2; I^2 = 0%; Analysis 2.6).
- *Diarrhoea (grade 2+):* Low-certainty evidence suggests that IMRT may be associated with less diarrhoea (RR 0.38, 95% CI 0.22 to 0.68; participants = 72; studies = 1; Analysis 2.7).
- *Vomiting (grade 2+)*: Moderate-certainty evidence suggests that there is probably little or no difference in the effect of IMRT and 3DCRT on vomiting (RR 0.60, 95% CI 0.29 to 1.24;

participants = 112; studies = 2; I^2 = 0%; Analysis 2.8)

- *Other review outcomes*: There were no data for meta-analysis on QoL or other review outcomes.

BT compared with EBRT

- *GI symptom scores*: One high-quality study (Nout 2009) reported findings on various bowel symptom domains at different time points. Substantial differences between BT and ERBT in favour of BT were found for 'limitation in daily activities due to bowel symptoms' (P < 0.001), faecal leakage (P < 0.001) and rectal blood loss (P = 0.04) at most time points up to five years post-radiotherapy; however these data were difficult to use in review meta-analysis due to the numerous time points and domains reported.
- *Acute GI toxicity (grade 2+):* We did not pool these subgroup data due to statistical heterogeneity. Evidence on acute grade 2+ toxicity from one study conducted among men with prostate cancer is of a very low certainty, mainly due to sparse data. However, evidence from a study among women with endometrial cancer (Nout 2009), indicates that BT for the treatment of early-stage endometrial cancer compared with EBRT reduces acute grade 2+ toxicity (RR 0.02, 95% CI 0.00 to 0.18; participants = 423; studies = 1; high-certainty evidence; Analysis 3.1) .
- *Late GI toxicity (grade 2+):* Low-certainty evidence suggests that there may be little or no difference in effects of BT and EBRT on late toxicity grade 2+ (RR 0.16, 95% CI 0.02 to 1.33; participants = 423; studies = 1; Analysis 3.2).
- *Quality of life:*Nout 2009 also reported data on QoL scores at various time points after radiotherapy to five years and found no clear difference in global health status between BT and EBRT groups at any time point; however, social functioning scores were significantly higher for the BT group (P = 0.005).
- *Other review outcomes*: There were no data on other review outcomes.

Other aspects of radiotherapy delivery

This group of studies comprises 10 diverse interventions, mostly evaluated in single small RCTs (13 studies altogether). We summarise the findings of four studies in Table 2, and consider them to have very low-certainty evidence in general. The following interventions had sufficient data on review outcomes and we used them in analyses:

Reduced radiation dose-volume

Reduced radiation dose volume compared with standard radiation dose volume.

Three studies (Arafat 2016; Gupta 2009; Huddart 2013) contributed data to toxicity outcomes; most data were derived from two studies (Arafat 2016; Huddart 2013) conducted in people undergoing RT for bladder cancer.

- *Acute GI toxicity:* Moderate-certainty evidence suggests that there is probably little or no difference in acute GI toxicity grade 2+ with reduced radiation dose volume (RR 1.21, 95% CI 0.81 to 1.81; participants = 211; studies = 1; Analysis 4.1) and low-certainty evidence suggests that there may be little or no difference in acute GI toxicity grade 1+ (RR 0.61, 95% CI 0.34 to 1.10; participants = 354; studies = 3; I^2 = 87%; Analysis 4.2).
- *Late GI toxicity:* Low-certainty evidence suggests that there may be little or no difference in late GI toxicity grade 2+ at one year (RR 1.02, 95% CI 0.15 to 6.97; participants = 107; studies = 1; Analysis 4.3) and two years post-radiotherapy (RR 0.38, 95% CI 0.04 to 3.48; participants = 79; studies = 1; Analysis 4.4), and little or no difference in late GI toxicity grade 1+ (RR 1.15, 95% CI 0.49 to 2.68; participants = 154; studies = 2; I^2 = 0%; Analysis 4.5).
- *Other review outcomes:* No evidence on QoL or other review outcomes was found.

Bladder-filling protocols

One study (Mullaney 2014) involving 110 participants compared a 1080 ml bladder-filling protocol with a 540 ml bladder-filling protocol.

- GI symptom scores: No evidence was found.
- *Acute GI toxicity:* Low-certainty evidence suggests that there may be little or no difference in a 1080 ml bladder-filling protocol compared with a 540 ml protocol on acute grade 2+ GI toxicity (RR 2.22, 95% CI 0.62 to 7.93; participants = 110; studies = 1; Analysis 5.1) and acute grade 1+ GI toxicity (RR 1.10, 95% CI 0.87 to 1.40; participants = 110; studies = 1; Analysis 5.2).
- *Late GI toxicity:* Low-certainty evidence suggests that there may be little or no difference in a 1080 ml bladder-filling protocol compared with a 540 ml protocol on late grade 2+ GI toxicity (RR 0.44, 95% CI 0.12 to 1.65; participants = 81; studies = 1; Analysis 5.3) and late grade 1+ GI toxicity (RR 0.83, 95% CI 0.51 to 1.37; participants = 81; studies = 1; Analysis 5.4).
- *Quality of life:* We were unable to extract data from the report for this outcome. However the authors stated that "There were no statistically significant associations between bladder filling preparations...and median QoL scores."
- *Other review outcomes*: There were no data on other review outcomes. This study also compared median comfort scores and reported "no statistically significant association" with the bladder-filling preparations.

Evening radiotherapy

Evening RT compared with morning RT

Two studies (Shukla 2010) involving 294 participants contributed data.

- *GI symptom scores:* No evidence was found.
- *Acute GI toxicity (grade 2+):* GI toxicity was evaluated in terms of diarrhoea during RT. Low-certainty evidence suggests that radiotherapy delivered in the evening may reduce acute GI toxicity (diarrhoea) grade 2+ during RT (RR 0.51, 95% CI 0.34 to 0.76; participants = 294; studies = 2; I^2 = 0%; Analysis 6.1) and grade 1+ GI toxicity (RR 0.78, 95% CI 0.68 to 0.89; participants = 294; studies = 2; I^2 = 0%; Analysis 6.2).
- *Diarrhoea:* see evidence on acute GI toxicity.
- *Other GI symptoms:* Evidence on vomiting is of a very low certainty (RR 0.43, 95% CI 0.09 to 2.18; participants = 229; studies = 1; Analysis 6.3).
- *Late GI toxicity:* We found no evidence on late toxicity.
- *Other review outcomes*: There were no data on QoL or other review outcomes.

Perineal hydrogel spacers

Hydrogel injection/spacer compared with no intervention

Two studies (Mariados 2015; Prada 2009) conducted in men undergoing RT for prostate cancer contributed data.

- *GI symptom scores:* No evidence was found.
- *Acute GI toxicity:* Low-certainty evidence suggests that hydrogel spacers may make little or no difference to acute GI (rectal) toxicity grade 2+ (RR 0.51, 95% CI 0.08 to 3.38; participants = 289; studies = 2; Analysis 7.1) and acute grade 1+ GI toxicity (RR 0.85, 95% CI 0.55 to 1.30; participants = 220; studies = 1; Analysis 7.2).
- *Late GI toxicity:* Low-certainty evidence suggests that hydrogel spacers may make little or no difference to late GI (rectal) toxicity grade 2+ up to 15 months post-RT (RR 0.16, 95% CI 0.01 to 3.96; participants = 220; studies = 1; Analysis 7.3) and at a median of three years (RR 0.07, 95% CI 0.00 to 1.34, participants = 140, studies = 1; Analysis 7.3). Evidence on late GI toxicity grade 1+ up to 15 months post-RT (RR 0.29, 95% CI 0.07 to 1.19; participants = 220; studies = 1; Analysis 7.4) and at a median of three years (RR 0.24, 95% CI 0.05 to 1.29; participants = 140; studies = 1; Analysis 7.4) is also low certainty.
- *Other GI symptoms:* Low-certainty evidence suggests that perineal hydrogel (spacer) may make little or no difference to late rectal bleeding (grade 1+) (RR 0.25, 95% CI 0.03 to 1.84; participants = 289; studies = 2; I^2 = 0%; Analysis 7.5). Evidence on acute rectal pain is of a very low certainty (RR 0.24, 95% CI 0.08 to 0.78; participants = 220; studies = 1; Analysis 7.6).
- *Quality of life*: We found no (continuous) data that could be included in meta-analysis. However, Prada 2009 included a bowel domain QoL question on rectal pain at six months and 12 months and reported 'statistically significant' reductions in favour of the hydrogel (P < 0.05). The other study (Mariados 2015) reported that fewer participants in the hydrogel group "reported declines in QoL relative to those of the control, with 11.6% and 21.4% of (hydrogel) and control patients, respectively, experiencing 10-point declines at 15 months" post-RT (P = 0.087). In the follow-up report of this study, which involved 63% of the original participants, at three years men in the spacer group were less likely to have a detectable change (five-point or 10-point reduction) in bowel QoL score on the expanded prostate cancer index composite (EPIC) scale than controls (five-point reduction: 41% versus 14%, P = 0.002; 10-point reduction: 21% versus 5%, P = 0.02).
- *Other review outcomes*: There were no data on other review outcomes. Late rectal urgency occurred in one participant in each arm of Mariados 2015, but these were classed as grade 1 events only.

Endorectal balloons (ERBs)

ERB compared with no intervention

Two studies (Botten 2015; Van Lin 2007) conducted among men undergoing RT for prostate cancer contributed data on toxicity outcomes.

- *GI symptom scores:* No evidence was found.
- *Acute GI toxicity:* Evidence on acute GI toxicity grade 2 + is of very low certainty (RR 1.00, 95% CI 0.41 to 2.42; participants = 48; studies = 1; Analysis 8.1). Low-certainty evidence suggests that ERBs may make little or no difference to acute GI toxicity grade 1+ (RR 0.95, 95% CI 0.70 to 1.29; participants = 48; studies = 1; Analysis 8.2).
- *Late GI toxicity:* Evidence on late GI toxicity grade 2 + is of very low certainty (RR 0.20, 95% CI 0.01 to 3.96; participants = 48; studies = 1; Analysis 8.3). Low-certainty evidence suggests that ERBs may reduce late grade 1 + GI toxicity (RR 0.31, 95% CI 0.14 to 0.72; participants = 48; studies = 1; Analysis 8.4)
- *Diarrhoea:* One study provided limited data on diarrhoea at one year post-RT and the evidence is of a very low certainty (RR 0.71, 95% CI 0.37 to 1.35; participants = 43; studies = 1; Analysis 8.5).
- *Other GI symptoms*: Evidence on acute rectal bleeding is of very low certainty (RR 5.00, 95% CI 0.25 to 98.96; participants = 48; studies = 1; Analysis 8.6). Low-certainty evidence suggests that ERBs may reduce late rectal bleeding (RR 0.53, 95% CI 0.25 to 1.09; participants = 91; studies = 2; I^2 = 0%).
- *Other review outcomes*: There were no data on QoL or other review outcomes.

Pharmacological interventions

The different types of pharmacological agents are listed in alphabetical order:

Anti-inflammatory agents

Aminosalicylates compared with placebo

- *Acute GI toxicity (grade 2+):* We analysed this by subgroup only because of differences in subgroup effects of the different aminosalicylic acid formulations (Test for subgroup differences: Chi^2 = 8.28, df = 1, P = 0.004, I^2 = 88.2%; Analysis 9.1). The evidence suggests that:
  - Mesalazine probably increases acute grade 2+ GI toxicity during RT (RR 1.22, 95% CI 1.02 to 1.45; participants = 143; studies = 2; I^2 = 15%; Analysis 9.1.1; moderate-certainty evidence);
  - Sulfasalazine may reduce acute grade 2+ GI toxicity during RT (RR 0.29, 95% CI 0.11 to 0.75; participants = 182; studies = 2; I^2 = 73%; Analysis 9.1.2; low-certainty evidence).
- It should also be noted that the mesalazine arm of a study from which data could not be extracted for this meta-analysis (Sanguineti 2003) was discontinued early following an unplanned interim analysis that indicated drug-related toxicity with rectally-administered mesalazine in seven out of the eight participants recruited to this study arm.
- *Late GI toxicity (grade 2+):* No data found/meta-analysis performed.
- *Acute GI symptom scores:* (diarrhoea only) were reported in one study of balsalazide versus placebo (Jahraus 2005) as having no statistically significant difference; however, these data lacked standard deviations and P values and could not be used in review analyses.
- *Diarrhoea (grade 2+):* As with the acute GI toxicity data, we did not pool these subgroup data. Subgroup findings suggest that some aminosalicylates, namely mesalazine and olsalazine, probably increase diarrhoea during RT (moderate-certainty evidence), whereas low-certainty evidence suggests that sulfasaline may have little or no effect on diarrhoea during RT:
  - Mesalazine: RR 1.55, 95% CI 1.14 to 2.10; participants = 191; studies = 2; I^2 = 0%; Analysis 9.3.1.
  - Osalazine: RR 1.70, 95% CI 1.00 to 2.87; participants = 58; studies = 1; Analysis 9.3.3. This study closed early due to increased diarrhoea grade 3/4 in the osalazine arm.
- Sulfasalazine: RR 0.80, 95% CI 0.41 to 1.59; participants = 171; studies = 2; I^2 = 69%; Analysis 9.3.2.
- *Other GI symptoms (grade 2+):* Low-certainty evidence suggests that aminosalicylates may have little or no effect on rectal bleeding during RT (RR 0.76, 95% CI 0.47 to 1.24; participants = 142; studies = 2; I^2 = 0%; Analysis 9.5) or up to three months after RT (RR 0.80, 95% CI 0.49 to 1.32; participants = 84; studies = 1; Analysis 9.6); it may have little or no effect on abdominal pain/cramps during RT (RR 1.08, 95% CI 0.50 to 2.33; participants = 261; studies = 3; I^2 = 54%; Analysis 9.7) or up to three months after RT (RR 0.16, 95% CI 0.01 to 3.04; participants = 54; studies = 1; Analysis 9.8); it may have little or no effect on tenesmus during RT (RR 2.10, 95% CI 0.73 to 6.03; participants = 142; studies = 2; I^2 = 3%; Analysis 9.9) and up to three months after RT (RR 0.38, 95% CI 0.02 to 9.04; participants = 54; studies = 1; Analysis 9.10); and it may have little or no effect on vomiting grade 2+ during RT (Analysis 9.11; Test for subgroup differences: Chi^2 = 3.05, df = 1, P = 0.08, I^2 = 67.3%; we therefore did not pool subgroup data). One study (Miller 2016) also reported data on grade 1+ abdominal pain after RT, which was more frequent in the sulfasalazine arm (32% versus 17%), and participants apparently discontinued the study medication as a result.
- *Medication for symptom control:* Moderate-certainty evidence based on pooled mesalazine and sulfasalazine subgroup data suggests that aminosalicylates probably increase the use of medication for symptom control (antidiarrhoeals) (RR 1.91, 95% CI 1.26 to 2.90; participants = 156; studies = 2; I^2 = 0%; Analysis 9.12).
- *Discontinuation of study medication:* Moderate-certainty evidence from Miller 2016 (sulfasalazine) suggests that aminosalicylates are probably more likely to be discontinued than placebo (RR 3.40, 95% CI 1.38 to 8.37; participants = 84; studies = 1; Analysis 9.13).
- No data on other review outcomes, including participant satisfaction and QoL, were found in the included studies.

Ibuprofen compared with no intervention

A single small study (Stryker 1979) contributed data, and the evidence is very uncertain (see Table 2).

Corticosteroids compared with placebo

One study (Fuccio 2011) of a beclomethasone dipropionate enema involving 114 men undergoing RT for prostate cancer contributed data to this comparison. Also relevant to this comparison is Sanguineti 2003, comparing a hydrocortisone enema with a sucralfate enema (study authors considered the latter to be equivalent to placebo). Outcomes in Fuccio 2011 were assessed cumulatively for the 12-month study duration. The effects of the rectally-administered corticosteroid compared with placebo were as follows:

- *Acute GI toxicity (grade 2+): We used* data from Sanguineti 2003 here, and downgraded them for indirectness. Low-certainty evidence suggests that there may be little or no difference between corticosteroid enemas and placebo on acute GI toxicity grade 2+ (RR 0.85, 95% CI 0.62 to 1.15; participants = 126; studies = 1; Analysis 10.1).
- *Late GI toxicity (grade 2+):* Low-certainty evidence suggests that corticosteroids may make little or no difference to GI

toxicity grade 2+ (RR 0.67, 95% CI 0.23 to 1.93; participants = 114; studies = 1; Analysis 10.2) or GI toxicity grade 1+ (RR 0.92, 95% CI 0.61 to 1.38; participants = 114; studies = 1; Analysis 10.3).

- *Late GI symptom scores:* The study authors presented data for mean change in IBDQ scores at one year graphically, with better scores in the corticosteroid arm (P = 0.034); however, we could not extract these data for meta-analysis.
- *Diarrhoea (grade 2+)*: Low-certainty evidence suggests that corticosteroids may make little or no difference to grade 2+ diarrhoea up to 12 months (RR 1.07, 95% CI 0.28 to 4.08; participants = 114; studies = 1; Analysis 10.4)
- *Other GI symptoms:* We acquired unpublished data from study authors for review purposes on rectal bleeding (RR 0.51, 95% CI 0.29 to 0.92; participants = 114; studies = 1; Analysis 10.5) and faecal urgency (any severity grade) (RR 0.91, 95% CI 0.44 to 1.85; participants = 114; studies = 1; Analysis 10.6), which suggests that rectally-administered corticosteroids may reduce rectal bleeding in the 12 months after radiotherapy (low-certainty evidence) but may have little or no effect on faecal urgency (low-certainty evidence).
- *Other review outcomes:* No data on QoL or other review outcomes were found in the included study.

Fuccio 2011 also evaluated rectosigmoidoscopy findings (see Potential biases in the review process section).

Superoxide dismutase (orgotein) compared with no intervention

Two studies evaluated this agent (Esco 2004; Menander-Huber 1978); however, only Esco 2004, with design limitations, contributed data to GI toxicity review outcomes:

- *Acute GI toxicity (grade 2+):* Low-certainty evidence suggests that superoxide dismutase may reduce grade 2+ GI toxicity (RR 0.20, 95% CI 0.05 to 0.86; participants = 92; studies = 1; Analysis 11.1).
- *Late GI toxicity (grade 2+):* The evidence on late effects at one year (RR 0.09, 95% CI 0.01 to 1.55; participants = 75; studies = 1; Analysis 11.2) and two years after radiotherapy (RR 0.06, 95% CI 0.00 to 1.11; participants = 68; studies = 1; Analysis 11.3) is very uncertain (i.e. very low-certainty evidence).
- *Other review outcomes:* There is a lack of data on other review outcomes, making the evidence on this anti-inflammatory agent very uncertain overall.

Amifostine

Amifostine compared with no intervention

Five studies evaluated amifostine (Athanassiou 2003; Katsanos 2010; Koukourakis 2000; Kouloulias 2005; Kouvaris 2003); however all studies had design limitations.

- *GI symptom scores:* No data for meta-analysis.
- *Acute GI toxicity (grade 2+):* This outcome was usually reported for the time point 'during RT'; however one study reported acute GI toxicity at 3 months' post-RT. Low-certainty evidence suggests that amifostine may reduce acute grade 2+ GI toxicity experienced during RT (RR 0.25, 95% CI 0.15 to 0.42; participants = 278; studies = 3; I^2 = 0%; Analysis 12.1). Evidence on acute grade 2+ GI toxicity at 3 months is of a very low certainty (RR 0.12, 95% CI 0.01 to 2.12; participants = 44).
- *Late GI toxicity (grade 2+):* Low-certainty evidence suggests that amifostine may have little or no effect on late grade 2+ GI toxicity (RR 1.48, 95% CI 0.64 to 3.45; participants = 249; studies = 2; I^2 = 0%; Analysis 12.4).
- *Diarrhoea (grade 2+):* The evidence on diarrhoea is very uncertain (RR 0.25, 95% CI 0.06 to 0.98; participants = 36; studies = 1; Analysis 12.6).
- *Other GI symptoms:* No evidence on other GI symptoms was found in the included studies.
- *Discontinuation of RT:* The evidence on discontinuation of RT with amifostine is very uncertain (RR 0.43, 95% CI 0.04 to 4.69; participants = 205; studies = 1; Analysis 12.7).
- *Discontinuation of amifostine:* This could not be meta-analysed because the control group received no intervention and data on discontinuation were reported for the experimental arms only. However, one study (Athanassiou 2003) reported that 3 participants had moderate to severe complications related to amifostine: two had severe hypotension and one had an allergic reaction; two of these patients discontinued amifostine. In another study (Koukourakis 2000), 4 participants in the amifostine arm had amifostine treatment interrupted due either to allergic reactions or severe weakness. Kouvaris 2003 reported that one participant had amifostine treatment interrupted due to an allergic reaction; in this study, 2/18 participants receiving amifostine had moderate hypotension. Similarly, side effects were also reported in Katsanos 2010 (2 participants had injection site erythema and pruritis and 2 participants had nausea and/or vomiting), however, this did not appear to lead to amifostine interruption or discontinuation.
- *Other interventions for symptom control: O*ne person in the amifostine arm of Athanassiou 2003 was reported to have had surgery for small bowel obstruction during the median follow up of 12 months.
- *Other review outcomes:* No data on other review outcomes, including QoL, were found in the included studies. Evidence from one study on acute grade 2+ GI toxicity according to route of administration (rectal or subcutaneous) of amifostine is of a very low-certainty (RR 0.32, 95% CI 0.01 to 7.55; participants = 53; Analysis 12.1).

Bile acid sequestrants

Bile acid sequestrants compared with placebo

Two small studies evaluated these agents (Chary 1984; Stryker 1983) and data were sparse. Most data are derived from Chary 1984, which compared cholestyramine with placebo. One outcome (medication for symptom control) includes data from Stryker 1983, which compared colestipol with no intervention:

- *GI symptom scores:* Evidence on GI symptom (diarrhoea) scores is of very low-certainty (MD 0.50, 95% CI -0.00 to 1.00; participants = 33; studies = 1; Analysis 13.1). These diarrhoea scores were based on an unvalidated investigator-designed scale.
- *Acute GI toxicity (grade 2+):* Low-certainty evidence suggests that bile acid sequestrants (cholestyramine) may increase grade 2+ GI toxicity (RR 4.24, 95% CI 1.07 to 16.70; participants = 33; studies = 1; Analysis 13.2).
- *Late GI toxicity (grade 2+):* No data for meta-analysis were found.
- *Diarrhoea (grade 2+):* Evidence on effect of bile acid sequestrants on diarrhoea is of very low-certainty (RR 2.82, 95% CI 0.66 to 12.01; participants = 33; studies = 1; Analysis 13.3)
- *Medication for symptom control:* The evidence on the effect of bile acid sequestrants on use of medication for symptom control is of a very low certainty (RR 2.49, 95% CI 0.29 to 21.34; participants = 64; studies = 2; I^2 = 77%; Analysis 13.4)
- *Discontinuation of study medication:* Meta-analysis was not possible for this outcome. However, Stryker 1983 reports that "Seven of the patients [in the intervention arm] ingested less than 70% of the prescribed dose and eight discontinued the drug. The most common reason given for discontinuing the drug was that it caused intestinal cramps."
- *Other review outcomes:* No evidence on QoL and other review outcomes was found.

The evidence on bile acid sequestrants is very uncertain overall.

Famotidine

We summarise findings from a small pilot study of famotidine compared with placebo (Razzaghdoust 2014) in Table 2.

Magnesium oxide

Magnesium oxide compared with placebo

One study (Lips 2011) contributed data on acute effects (during RT) of oral magnesium oxide compared with placebo.

- *GI symptom scores:* No data for meta-analysis were found.
- *Acute GI toxicity (grade 2+):* Moderate-certainty evidence suggests that magnesium oxide probably does not reduce acute GI toxicity grade 2+ and may increase it (RR 1.70, 95% CI 0.87 to 3.31; participants = 92; studies = 1; Analysis 14.1).
- *Late GI toxicity (grade 2+):* No data for meta-analysis were found.
- *Diarrhoea (grade 2+):* No data for meta-analysis were found.
- *Medication for symptom control:* Low-certainty evidence suggests that magnesium oxide may make little or no difference to use of medication for symptom control (RR 1.75, 95% CI 0.55 to 5.57; participants = 92; studies = 1; Analysis 14.2).
- *Discontinuation of study medication:* Low-certainty evidence suggests that magnesium oxide may make little or no difference to discontinuation of study medication (RR 4.00, 95% CI 0.46 to 34.44; participants = 92; studies = 1; Analysis 14.3).
- *Quality of life:* This was presented graphically in the Lips 2011 report and findings were interpreted by the authors as "a trend towards worsened QoL" in the magnesium oxide arm.
- *Other review outcomes*: No data for meta-analysis were found.

The limited evidence above suggests the potential for harm with oral magnesium oxide administered prophylactically during RT in men with prostate cancer.

Misoprostol

Misoprostol suppository compared with placebo

One study (Hille 2005) comparing a misoprostol rectal suppository (400 μg) with placebo contributed acute-phase data to this comparison. A follow-up study in 2009 reported late effects at a median follow-up of 50 months (9 to 59 months).

- *GI symptom scores:* No data for meta-analysis were found.
- *Acute GI toxicity (grade 2+):* Low-certainty evidence suggests that misoprostol may make little or no difference to acute GI toxicity grade 2+ during RT (RR 1.38, 95% CI 0.76 to 2.51; participants = 100; studies = 1; Analysis 15.1).
- *Late GI toxicity (grade 2+):* No data for meta-analysis were found.
- *Diarrhoea (grade 2+):* Evidence on acute (RR 1.00, 95% CI 0.46 to 2.19; participants = 100; studies = 1; Analysis 15.2) and late diarrhoea (RR 2.00, 95% CI 0.19 to 21.36; participants = 100; studies = 1; Analysis 15.3) is of a very low certainty.
- *Other GI symptoms:* Moderate-certainty evidence suggests that misoprostol probably increases acute rectal bleeding (RR 2.29, 95% CI 1.03 to 5.07; participants = 100; studies = 1; Analysis 15.4), but the evidence on late rectal bleeding is very uncertain (RR 4.00, 95% CI 0.46 to 34.54; participants = 100; studies = 1; low-certainty evidence; Analysis 15.5). Evidence on other GI symptoms is very uncertain, mainly due to sparse data, including acute tenesmus (RR 1.60, 95% CI 0.56 to 4.56; participants = 100; studies = 1; Analysis 15.6), late tenesmus (RR 2.00, 95% CI 0.19 to 21.36; participants = 100; studies = 1; Analysis 15.7), acute faecal urgency (RR 1.50, 95% CI 0.67 to 3.35; participants = 100; studies = 1; Analysis 15.8), late faecal incontinence (RR 1.00, 95% CI 0.06 to 15.55; participants = 100; studies = 1; Analysis 15.9), and acute abdominal pain or

cramps (RR 1.60, 95% CI 0.56 to 4.56; participants = 100; studies = 1; Analysis 15.10).

- *Other review outcomes*: No evidence on QoL or other review outcomes was found.

The limited evidence above suggests the potential for harm with misoprostol suppositories administered prophylactically during RT in men with prostate cancer.

Octreotide

Octreotide acetate injection compared with placebo

Two studies contributed data (Martenson 2008; Zachariah 2010).

- *GI symptom scores:* No data for meta-analysis were found. Also see QoL outcome below.
- *Acute GI toxicity (grade 2+):* No data for meta-analysis were found.
- *Late GI toxicity (grade 2+):* No data for meta-analysis were found.
- *Acute diarrhoea (grade 2+):* Moderate-certainty evidence suggests that there may be little or no difference in acute diarrhoea grade 2+ with octreotide (RR 1.01, 95% CI 0.76 to 1.35; participants = 340; studies = 2; I^2 = 33%; Analysis 16.1).
- *Other GI symptoms:* Moderate-certainty evidence suggests that octreotide probably increases acute rectal bleeding (RR 1.65, 95% CI 1.21 to 2.24; participants = 340; studies = 2; I^2 = 0%; Analysis 16.2). Low-certainty evidence on other GI symptoms suggests that there may be little or no difference between octreotide and placebo on acute tenesmus (RR 2.29, 95% CI 0.74 to 7.04; participants = 125; studies = 1; Analysis 16.3), vomiting (RR 0.89, 95% CI 0.48 to 1.66; participants = 125; studies = 1;Analysis 16.4), abdominal pain/cramps (RR 2.29, 95% CI 0.74 to 7.04; participants = 125; studies = 1; Analysis 16.5), and faecal incontinence (RR 1.34, 95% CI 0.87 to 2.06; participants = 125; studies = 1; Analysis 16.6).
- *Medication for symptom control*: Moderate-certainty evidence suggests that there may be little or no difference in this outcome (RR 1.03, 95% CI 0.83 to 1.28; participants = 219; studies = 1; Analysis 16.7).
- *Discontinuation of study medication:* This evidence is of a very low certainty (RR 1.30, 95% CI 0.30 to 5.66; participants = 219; studies = 1; Analysis 16.8).
- *Quality of life*: We could not extract these data from the reports. However, one study (Zachariah 2010) stated that "We did not observe a statistically significant difference between treatment groups in the proportion of patients who reported improved QoL or bowel function at 3 months (among evaluable patients) in any of the four assessments". The other study (Martenson 2008) reported that median QoL scores were similar, as measured on a scale of 0 to 10 (7.8 versus 7.7 for octreotide and placebo groups, respectively) (P = 0.29).

The limited evidence above suggests the potential for harm with octreotide administered prophylactically to people undergoing RT for pelvic cancer.

Selenium

Oral selenium compared with no intervention

Only one study contributed data to this comparison (Muecke 2010).

- *Acute diarrhoea (grade 2+) during RT:* Low-certainty evidence suggests that oral selenium may have little or no effect on this outcome (RR 0.40, 95% CI 0.12 to 1.41; participants = 81; studies = 1; Analysis 17.1).
- *Other review outcomes*: No evidence on other review outcomes was found.

Smectite

Smectite compared with placebo

One study (Hombrink 2000) involving 176 people with various pelvic cancers evaluated this comparison; however, we could extract no usable data for meta-analysis. Details and findings of this study are described in Table 2.

Sodium butyrate

Sodium butyrate enemas compared with placebo

One study (Maggio 2014) evaluated three different doses of sodium butyrate enemas versus placebo in men with prostate cancer. We combined the data for the different doses and compared them with placebo, as tests for subgroup differences indicated that there was no difference between these subgroup findings.

- *Acute GI toxicity:* Moderate-certainty evidence suggests that sodium butyrate enemas probably make little or no difference to grade 2+ acute GI toxicity (RR 0.91, 95% CI 0.41 to 1.98; participants = 162; studies = 1; Analysis 18.1) and grade 1+ acute GI toxicity (RR 1.08, 95% CI 0.61 to 1.91; participants = 157; studies = 1; Analysis 18.2).
- *Other review outcomes*: No evidence on other review outcomes was found.

This study also evaluated rectosigmoidoscopy findings (see Potential biases in the review process section of the Discussion).

Simethicone

A single small study (McGuffin 2016) was reported as a conference abstract and the evidence is very uncertain (see Table 2).

Sucralfate

Oral sucralfate compared with placebo

- *GI symptom scores:* No data for meta-analysis.
- *Acute GI toxicity (grade 2+):* Moderate-certainty evidence suggests that oral sucralfate probably has little or no effect on acute GI toxicity grade 2+ (RR 1.07, 95% CI 0.83 to 1.39; participants = 335; studies = 1; Analysis 19.1) or on acute grade 1+ toxicity (RR 1.04, 95% CI 0.95 to 1.13; participants = 335; studies = 1; Analysis 19.2).
- *Late GI toxicity (grade 2+):* Moderate-certainty evidence suggests that sucralfate probably has little or no effect on late GI toxicity grade 2+ (RR 0.76, 95% CI 0.51 to 1.14; participants = 298; studies = 1; Analysis 19.3).
- *Diarrhoea (grade 2+):* Low-certainty evidence suggests that sucralfate may have little or no effect on acute diarrhoea grade 2+ (RR 0.81, 95% CI 0.41 to 1.62; participants = 284; studies = 4; I^2 = 82%; Analysis 19.4).
- *Other GI symptoms (grade 2+):* Oral sucralfate may increase acute rectal bleeding (RR 1.32, 95% CI 1.10 to 1.60; participants = 604; studies = 4; I^2 = 0%; Analysis 19.5; *low-certainty evidence*), but probably has little or no effect on abdominal pain/cramps (RR 0.97, 95% CI 0.58 to 1.60; participants = 269; studies = 3; I^2 = 0%; Analysis 19.6*moderate-certainty evidence*) and may have little or no effect on faecal urgency (RR 1.14, 95% CI 0.93 to 1.40; participants = 123; studies = 1; Analysis 19.7; *low-certainty evidence*) or tenesmus (RR 3.44, 95% CI 0.74 to 15.92; participants = 123; studies = 1; Analysis 19.9; *low-certainty evidence*). Low-certainty evidence suggests that faecal incontinence may be increased with oral sucralfate (RR 2.07, 95% CI 1.06 to 4.02; participants = 123; studies = 1; I^2 = 0%; Analysis 19.8).
- *Medication for symptom control:* Low-certainty evidence suggests that oral sucralfate may make little or no difference to use of medication for symptom control (RR 0.84, 95% CI 0.49 to 1.42; participants = 313; studies = 4; I^2 = 58%; Analysis 19.10).
- *Discontinuation of study medication:* Moderate-certainty evidence suggests that there is probably little or no difference between oral sucralfate and placebo in discontinuation rates (RR 1.02, 95% CI 0.48 to 2.18; participants = 348; studies = 4; I^2 = 17%; Analysis 19.11).
- *Quality of life:* no evidence found.

Rectal sucralfate (enema) compared with placebo

- *GI symptom scores:* No data for meta-analysis.
- *Acute GI toxicity (grade 2+):* Low-certainty evidence suggests that rectal sucralfate may have little or no effect on acute GI toxicity grade 2+ (RR 1.18, 95% CI 0.87 to 1.60; participants = 126; studies = 1; Analysis 19.1).
- *Late GI toxicity (grade 2+):* No data for meta-analysis.
- *Diarrhoea (grade 2+):* Low-certainty evidence suggests that rectal sucralfate may have little or no effect on acute diarrhoea grade 2+ (RR 0.82, 95% CI 0.44 to 1.53; participants = 83; studies = 1; Analysis 19.4).
- *Other GI symptoms (grade 2+):* Evidence on acute rectal bleeding (RR 0.87, 95% CI 0.61 to 1.24; participants = 83; studies = 1; Analysis 19.5); pain/cramps (RR 1.02, 95% CI 0.15 to 6.93; participants = 83; studies = 1; Analysis 19.6); faecal urgency (RR 1.02, 95% CI 0.52 to 2.01; participants = 83; studies = 1; Analysis 19.7); faecal incontinence (RR 0.68, 95% CI 0.12 to 3.88; participants = 83; studies = 1; Analysis 19.8); and tenesmus (RR 0.98, 95% CI 0.69 to 1.41; participants = 83; studies = 1; Analysis 19.9) is of a very low-certainty.
- *Other review outcomes*: No evidence is available on QoL or other review outcomes.

Tropisetron

Findings from this single small study (Kardamakis 1995) are summarised in Table 2.

Non-pharmacological interventions

Diet

Elemental diet compared with usual diet

Data on review outcomes were sparse for this dietary intervention (we could only extract data on GI symptom scores and QoL) and were derived from one small study (McGough 2008; 50 participants). This evidence is based on unpublished findings from week three of RT.

- *GI symptom score (IBDQ-B)*: Low-certainty evidence suggests that IBDQ-B scores with an elemental diet (during RT)) may be worse than with usual diet (MD -5.80, 95% CI -11.32 to -0.28; Analysis 20.6.2) (high scores are better, with a maximum of 70 and minimum of 10).
- *Diarrhoea during RT:* Low-certainty evidence suggests that an elemental diet may make little or no difference to diarrhoea grade 2+ (RR 0.79, 95% CI 0.45 to 1.38; participants = 50; studies = 1; Analysis 20.5).
- *Quality of life (IBDQ):* Low-certainty evidence suggests that there may be little or no difference in QoL scores during RT

with an elemental diet (MD 4.60, 95% CI -12.40 to 21.60; participants = 50; studies = 1; Analysis 20.11) (high scores are better, with a maximum of 224 and minimum of 32).

- *Other review outcomes:* No evidence on other review outcomes was found.

Lactose-restricted diet compared with usual diet

Two studies evaluated a lactose-restricted diet (Stryker 1986; Pettersson 2012) but only the latter contributed data to meta-analysis. This study evaluated a lactose-restricted plus low insoluble fibre diet.

- *Acute GI toxicity:* Low-certainty evidence suggests that a lactose-restricted diet may make little or no difference to acute GI toxicity grade 1+ (RR 0.89, 95% CI 0.62 to 1.27; participants = 119; studies = 1; Analysis 20.2.1). There were no reported instances of grade 2+ acute GI toxicity.
- *Late GI toxicity:* Low-certainty evidence suggests that a lactose-restricted diet may make little or no difference to late GI toxicity grade 1+ (RR 0.99, 95% CI 0.64 to 1.53; participants = 106; studies = 1; Analysis 20.3.1). There were no reported instances of grade 2+ late GI toxicity.
- *Diarrhoea during RT:* Low-certainty evidence suggests that a lactose-restricted diet may make little or no difference to diarrhoea grade 1+ (RR 0.74, 95% CI 0.45 to 1.23; participants = 119; studies = 1; Analysis 20.4.1).
- *Quality of life:* QoL was reported using QLQ-PR25 for many time points and domains up to 24 months post-RT, with study authors finding little difference between study arms at any time point; however we could not extract these data in a usable way.
- *Other review outcomes:* No evidence on other review outcomes was found.

Stryker 1986 reported weekly stool frequency (instead of diarrhoea) and found no difference between a lactose-restricted diet and a usual diet for this outcome, or in the number of anti-diarrhoeal tablets taken by participants in each group each week. This study contributed no usable data to review outcomes.

High-fibre diet compared with usual diet

Three studies of different high-fibre interventions contributed data (Itoh 2015 - hydrolysed rice bran; Murphy 2000 - psyllium husk; Wedlake 2017 - fibre > 18 g/day). The resulting evidence is mainly of a low to very low certainty.

- *GI symptom scores:* Low-certainty evidence from one study suggests that a high-fibre diet may make little difference to GI symptom scores (IBDQ-B) at the end of RT (MD 2.80, 95% CI -1.81 to 7.41; participants = 108; studies = 1; Analysis 20.6.3), but may improve GI symptom scores at one year post-RT (MD 6.10, 95% CI 1.71 to 10.49; participants = 108; studies = 1; Analysis 20.7.2). In addition, low-certainty findings suggest that a high-fibre diet may be associated with less of a change in IBDQ-B symptom scores from baseline at the end of RT (MD 7.10, 95% CI 2.14 to 12.06; participants = 108; studies = 1; Analysis 20.8) and at one year post-RT (MD 8.50, 95% CI 3.25 to 13.75; participants = 108; studies = 1; Analysis 20.9.1) compared with usual diet.
- *Diarrhoea during RT*: Low-certainty evidence suggests that high fibre may make little or no difference to diarrhoea grade 2+ (RR 0.65, 95% CI 0.38 to 1.10; participants = 74; studies = 2; I^2 = 0%; Analysis 20.5.3) or grade 1+ (RR 1.00, 95% CI 0.94 to 1.07; participants = 74; studies = 2; Analysis 20.4.2).
- *Quality of life (IBDQ)*: Low-certainty evidence suggests that there may be little or no difference in QoL scores during RT with a high-fibre diet (MD 6.50, 95% CI -5.88 to 18.88; participants = 108; studies = 1; Analysis 20.11.1); however, it may improve QoL scores at one year after RT (MD 20.50, 95% CI 9.97 to 31.03; participants = 108; studies = 1; Analysis 20.12.1; *low-certainty evidence*).
- *Medication for symptom control:* Meta-analysis was not possible for this outcome. Wedlake 2017 reported the number of days upon which medication was used (according to self-reported participant diaries): use of median scores masks differences in individuals' usage; median scores in both groups were 0 (with ranges 0 - 7 in both groups). The small study on hydrolysed rice bran (Itoh 2015) also reported an 'anti-diarrhoeal agent score' based on administration of probiotics and antidiarrhoeal agents; however, these results are difficult to interpret.
- *Other review outcomes:* No evidence on other review outcomes was found.

Low-fibre diet compared with usual diet

One study contributed data (Wedlake 2017).

- *GI symptom scores:* Low-certainty findings suggest that a low-fibre diet may make little or no difference to GI symptom scores at the end of RT (MD 3.50, 95% CI -0.93 to 7.93; participants = 107; studies = 1; Analysis 20.6.4) or at one year after RT (MD 3.30, 95% CI -0.94 to 7.54; participants = 107; studies = 1; Analysis 20.7.2). Low-certainty evidence on the change in IBDQ-B symptom scores from baseline at the end of RT and at one year also suggests little or no difference with low fibre compared with usual diet (Analysis 20.8 and Analysis 20.9).
- *Acute GI toxicity:* Low-certainty evidence suggests that there may be little or no difference in acute GI toxicity grade 1+ with a low-fibre diet (RR 0.89, 95% CI 0.62 to 1.27; participants = 119; studies = 1; Analysis 20.2.2). There were no reported instances of grade 2+ acute GI toxicity.
- *Late GI toxicity:* Low-certainty evidence suggests that a low-fibre diet may make little or no difference to late GI toxicity grade 1+ (RR 0.99, 95% CI 0.64 to 1.53; participants = 106; studies = 1; Analysis 20.3). There were no reported instances of grade 2+ acute GI toxicity.

- *Diarrhoea during RT*: Low-certainty evidence suggests that a low-fibre diet may make little or no difference to diarrhoea grade 1+ during RT (RR 0.74, 95% CI 0.45 to 1.23; participants = 119; studies = 1; Analysis 20.4.3).
- *Quality of life (IBDQ)*: Low-certainty evidence suggests that a low-fibre diet may make little or no difference to QoL scores during RT (MD 9.80, 95% CI -1.91 to 21.51; participants = 107; studies = 1; Analysis 20.11.2) or at one year after RT (MD 9.40, 95% CI -1.78 to 20.58; participants = 107; studies = 1; Analysis 20.12).
- *Other review outcomes:* No evidence on other review outcomes was found.

Low-fat diet compared with usual diet

One study contributed data to this comparison (Wedlake 2012).

- *Acute GI toxicity grade 2+*: Low-certainty evidence suggests that a low-fat diet may make little or no difference to acute GI toxicity grade 2+ (RR 1.15, 95% CI 0.71 to 1.84; participants = 79; studies = 1; Analysis 20.1).
- *GI symptom scores (Vaizey scale):* Low-certainty evidence suggests that a low-fat diet may make little or no difference to GI symptom scores (MD -0.20, 95% CI -2.29 to 1.89; participants = 70; studies = 1; Analysis 20.6.1).
- *Diarrhoea during RT*: Low-certainty evidence suggests that a low-fat diet may make little or no difference to diarrhoea grade 2+ during RT (RR 0.61, 95% CI 0.33 to 1.13; participants = 76; studies = 1; Analysis 20.5.2).
- *Quality of life (IBDQ)*: Low-certainty evidence suggests that a low-fat diet may make little or no difference to QoL scores (MD 2.40, 95% CI -9.52 to 14.32; participants = 76; studies = 1; Analysis 20.11.3).
- *Other review outcomes:* No evidence on other review outcomes was found.

Prebiotic diet compared with usual diet

One study (Garcia-Peris 2016) evaluated prebiotics in addition to the usual on-treatment diet (low-fibre, lactose-restricted), compared with the usual on-treatment diet; however, data were not in a usable form for review meta-analyses. The prebiotic group experienced a decrease in the number of days with watery stools compared with the control group (P = 0.08). The study also reported "no significant difference" in global health scores and symptom scores, including diarrhoea, nausea/vomiting and pain, and antidiarrhoeal use (loperimide).

Counselling

Counselling (dietary or other) compared with no intervention

Two studies (Kim 2002; Ravasco 2005) contributed data on counselling interventions.

- *GI symptom scores:* Low-certainty evidence from one study (Kim 2002) suggests that counselling may have little or no effect on GI symptom scores (MD 0.08, 95% CI -0.38 to 0.54; participants = 152; Analysis 21.1). However, Ravasco 2005 reported that diarrhoea scores significantly deteriorated from baseline to end of RT in the control group but did not do so in the counselling group. With insufficient data, it was not possible to perform meta-analysis.
- *Acute GI toxicity grade 2+:* No evidence was found (see diarrhoea grade 2+ below).
- *Late GI toxicity (grade 2+):* No evidence was found (see diarrhoea grade 2+ below).
- *Diarrhoea (grade 2+):* Low-certainty evidence suggests that counselling may have reduce diarrhoea grade 2 + during RT (RR 0.12, 95% CI 0.03 to 0.47; participants = 74; studies = 1; Analysis 21.2), at three months post-RT (RR 0.04, 95% CI 0.00 to 0.60; participants = 74; studies = 1; Analysis 21.3) and at five year post-RT (RR 0.05, 95% CI 0.00 to 0.78; participants = 61; studies = 1; Analysis 21.4).

- *Other GI symptoms*: Evidence on the effect of counselling on weight loss at the end of RT is of a very low certainty (RR 0.76, 95% CI 0.44 to 1.34; participants = 74; studies = 1; Analysis 21.5); however, counselling may reduce nausea and vomiting at the end of RT (RR 0.44, 95% CI 0.20 to 0.94; participants = 74; studies = 1; Analysis 21.7). Counselling may reduce weight loss at three months post-RT (RR 0.10, 95% CI 0.01 to 0.74; participants = 74; studies = 1; Analysis 21.8; *low-certainty evidence*). Evidence on nausea and vomiting at three months after RT is of a very low certainty (RR 0.08, 95% CI 0.00 to 1.32; participants = 74; studies = 1; Analysis 21.8).
- *Medication for symptom control*: Counselling may reduce the use of medication (anti-diarrhoeals) for symptom control at the end of RT (RR 0.10, 95% CI 0.03 to 0.31; participants = 74; studies = 1; Analysis 21.9; *low-certainty evidence*) and at three months post-RT (RR 0.02, 95% CI 0.00 to 0.39; participants = 74; studies = 1; Analysis 21.10).
- *Quality of life*: Evidence on QoL, derived from one study (Kim 2002), is of a low certainty. This study evaluated QoL according to a five-point visual analogue scales for single items, the findings of which suggest that counselling may reduce fatigue (MD -0.41, 95% CI -0.83 to 0.01; participants = 152; studies = 1; Analysis 21.11.1) and sleeping problems (MD -0.46, 95% CI -0.89 to -0.03; participants = 152; studies = 1; Analysis 21.11.2) (lower scores mean better). Similarly, Ravasco 2005 reported that "at 3 months, Group I [counselling group] patients maintained/improved function, symptoms and single-item scores (P<0.02)" compared with baseline scores, whereas in the control group "QoL remained as poor as after radiotherapy".

Protein supplement compared with no intervention

One study contributed data (Ravasco 2005).

- *GI symptom scores:* There were insufficient data to analyse (mean scores were reported without standard deviations or P values). However, diarrhoea scores significantly deteriorated from baseline to end of RT in both the protein supplement and the control groups, and mean diarrhoea scores were similar at three-month follow-up (72 and 78 for supplement and control, respectively).
- *Acute GI toxicity grade 2+:* No evidence was found (see diarrhoea grade 2+ below).
- *Late GI toxicity (grade 2+):* No evidence was found (see diarrhoea grade 2+ below).
- *Diarrhoea (grade 2+):* Protein supplements may reduce diarrhoea at three months post-RT (RR 0.23, 95% CI 0.07 to 0.74; participants = 74; studies = 1; *low-certainty evidence;* Analysis 22.2). Evidence on diarrhoea at other time points is very uncertain: end of RT (RR 0.53, 95% CI 0.27 to 1.03; participants = 74; studies = 1; Analysis 22.1; *very low-certainty evidence*); five years post-RT (RR 0.60, 95% CI 0.23 to 1.51; participants = 61; studies = 1; Analysis 22.3; *very low-certainty evidence*).
- *Other GI symptoms*: Evidence is of a very low certainty for effects on vomiting at the end of RT (RR 0.63, 95% CI 0.33 to 1.19; participants = 74; studies = 1; Analysis 22.4) and at three months post-RT (RR 0.50, 95% CI 0.14 to 1.85; participants = 74; studies = 1; Analysis 22.5). Similarly, evidence on weight loss at the end of RT is of a very low certainty (RR 0.82, 95% CI 0.48 to 1.41; participants = 74; studies = 1). However, at three months weight loss may be reduced with protein supplements (RR 0.30, 95% CI 0.09 to 1.00; participants = 74; studies = 1; Analysis 22.7; *low-certainty evidence*).
- *Medication for symptom control*: Protein supplements may reduce use of medication for symptom control at the end of RT (RR 0.69, 95% CI 0.49 to 0.97; participants = 74; studies = 1; Analysis 22.8; *low-certainty evidence*) and at three months post-RT (RR 0.30, 95% CI 0.14 to 0.66; participants = 74; studies = 1; Analysis 22.9; *low-certainty evidence*).
- *Quality of life*: There were insufficient data to analyse. Mean global QoL scores (without standard deviations) were reported to be significantly different (better) compared with baseline scores in the protein supplement group at the end or RT and at three months post-RT, but were significantly worse than baseline scores at these time points in the control group. In addition, a few function and single-item symptom scores (measured on five-point visual analogue scales) improved at the end of three months in the protein supplement group, whereas in the control group all QoL domains remained as poor at the three-month follow-up as at the end of RT.

Glutamine

Glutamine compared with placebo

Five studies contributed data (De Maria 1992; Kozelsky 2003; Manir 2014; Rotovnik Kozjek 2011; Vidal-Casariego 2014).

- *GI symptom scores:* no evidence was found for this outcome.
- *Acute GI toxicity (grade 2+):* Low-certainty evidence suggests that glutamine may have little or no effect on acute GI toxicity grade 2+ (RR 2.40, 95% CI 0.68 to 8.53; participants = 69; studies = 1; Analysis 23.1) or grade 1+ (RR 1.72, 95% CI 0.70 to 4.20; participants = 69; studies = 1; Analysis 23.2) during RT.
- *Late GI toxicity (grade 2+):* Low-certainty evidence suggests that glutamine may have little or no effect on late GI toxicity grade 2+ (RR 4.52, 95% CI 0.23 to 90.80; participants = 57; studies = 1; Analysis 23.3) or grade 1+ (RR 1.50, 95% CI 0.40 to 5.69; participants = 57; studies = 1; Analysis 23.4) at one year post-RT.
- *Diarrhoea (grade 2+):* High-certainty evidence indicates that glutamine has little or no effect on diarrhoea grade 2+ during RT (RR 0.98, 95% CI 0.78 to 1.24; participants = 287; studies = 4; I^2 = 0%; Analysis 23.5).
- *Other GI symptoms (grade 2+):* Low-certainty evidence suggests that glutamine may have little or no effect on tenesmus (RR 2.23, 95% CI 0.82 to 6.07; participants = 129; studies = 1; Analysis 23.6); abdominal pain/cramps (RR 0.97, 95% CI 0.58 to 1.60; Analysis 23.7); rectal bleeding (RR 1.02, 95% CI 0.51 to 2.02; participants = 129; studies = 1; Analysis 23.8), vomiting (RR 1.02, 95% CI 0.32 to 3.28; participants = 85; studies = 1; Analysis 23.9) or nausea (RR 1.37, 95% CI 0.32 to 5.73; participants = 85; studies = 1; Analysis 23.10) during RT or faecal incontinence (Analysis 23.12) during RT. Similarly findings from a single study with follow up at one and two years post RT suggests that glutamine may make little or no difference to faecal incontinence (Analysis 23.13, Analysis 23.14), to abdominal pain or cramps (Analysis 23.16; Analysis 23.17), or to rectal bleeding (Analysis 23.18; Analysis 23.19), at one and two years post RT, respectively.
- *Medication for symptom control:* Low-certainty evidence suggests that glutamine may increase the use of medication for symptom control (RR 2.82, 95% CI 1.05 to 7.58; participants = 198; studies = 2; I^2 = 0%; Analysis 23.11).
- *Discontinuation of study medication:* no evidence was found.
- *Quality of life:* One study (Kozelsky 2003) reported similar median QoL scores in the glutamine and placebo arms at 12 months (P = 0.94) and 24 months (P = 0.13), respectively; however, these data were not in a usable form for our meta-analysis. Study authors concluded that "Quality-of-life scores and the mean number of problems reported on the bowel function questionnaire were virtually identical for both treatment groups."

Probiotics

Probiotics compared with control (placebo or no intervention)

Most studies compared probiotics with placebo (Chitapanarux 2010; Delia 2007; Demers 2014; Giralt 2008; Nascimento 2014), but two studies compared probiotics with no probiotics (Salminen 1988; Timko 2013), and one three-arm study compared probiotics with probiotics plus honey or placebo (Mansouri-Tehrani 2016). For the latter study, we combined data for the two probiotic arms. Doses (colony-forming units) and strains of probiotic preparations varied across studies, and usable data were generally sparse, such that subgrouping according to these variables was not possible.

- *GI symptom scores:* No evidence for meta-analysis was found. One small pilot study (Nascimento 2014; 20 participants) of synbiotics (probiotics plus prebiotics) reported GI symptom scores (using EORTC QLQ PR23) as medians (IQR); median scores were lower with probiotics during the second week of treatment (16.5, IQR 15 - 23) than with placebo (19.5, IQR 15 - 26) ($P < 0.05$) and in the third week of treatment ($P < 0.01$).
- *Acute GI toxicity (grade 2+):* No evidence was found on acute GI toxicity grade 2+, but most studies reported acute diarrhoea grade 2+ (see below).
- *Late GI toxicity (grade 2+):* No evidence was found.
- *Diarrhoea (grade 2+):* Low-certainty evidence suggests that probiotics may reduce acute diarrhoea grade 2+ during or at the end of RT (RR 0.43, 95% CI 0.22 to 0.82; participants = 923; studies = 5; I^2 = 91%; Analysis 24.1).
- *Other GI symptoms (grade 2+):* The evidence on weight loss is of a very low certainty (RR 0.91, 95% CI 0.37 to 2.23; participants = 21; studies = 1; Analysis 24.2); no evidence on other symptoms was found.
- *Medication for symptom control:* Low-certainty evidence suggests that probiotics may reduce the use of medication for symptom control (RR 0.53, 95% CI 0.32 to 0.88; participants = 507; studies = 6; I^2 = 57%; Analysis 24.3).
- *Discontinuation of study medication:* no evidence was found.
- *Quality of life:* No evidence was found for meta-analysis. One small pilot study (Nascimento 2014; 20 participants) of synbiotics (probiotics plus prebiotics) reported better (lower) median QoL scores for proctitis (using EORTC QLQ PR23) with probiotics during the second week of treatment (23, IQR 21 - 30) than with placebo (26.5, IQR 22 - 34) ($P < 0.05$) and in the third week of treatment ($P < 0.01$).

Proteolytic enzymes

Two studies contributed data (Dale 2001; Martin 2002); Martin 2002 compared oral proteolytic enzymes with placebo and Dale 2001 compared the enzymes with no intervention.

- *GI symptom scores:*Dale 2001 evaluated mean RTOG scores, which could not be used in a meaningful way in this review.
- *Acute GI toxicity:* Low-certainty evidence suggests that proteolytic enzymes may reduce acute GI toxicity grade 2+ (RR 0.45, 95% CI 0.24 to 0.88; participants = 120; studies = 1; Analysis 25.1); but not grade 1 toxicity (acute GI toxicity grade 1+: RR 1.04, 95% CI 0.91 to 1.18; participants = 120; studies = 1; Analysis 25.2).
- *Late GI toxicity (grade 2+):* No evidence was found.
- *Diarrhoea (grade 2+):* The evidence on diarrhoea grade 2+ during RT is of a very low certainty (RR 1.60, 95% CI 0.89 to 2.89; participants = 56; studies = 1; Analysis 25.3).
- *Other GI symptoms (grade 2+):* Evidence on vomiting (RR 0.33, 95% CI 0.01 to 7.85; participants = 56; studies = 1; Analysis 25.4) and rectal bleeding (RR 1.00, 95% CI 0.21 to 4.76; participants = 120; studies = 1; Analysis 25.5) is of a very low certainty.
- *Medication for symptom control:* Low-certainty evidence suggests that proteolytic enzymes may increase the use of medication for diarrhoea symptom control (RR 2.00, 95% CI 1.21 to 3.30; participants = 56; studies = 1; Analysis 25.6).
- *Other review outcomes:* No evidence on QoL or other review outcomes was found.

The evidence overall is of a low to very low certainty; and evidence from one small study suggests a potential for harm.
Another type of enzyme (lactase) was evaluated in an older study (Stryker 1986), but we could extract no data for review outcomes. Authors reported no clear difference between the lactase group and other study groups in mean weekly stool frequency and anti-diarrhoeals taken by participants. More details about this study can be found in Table 2.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

IMRT compared with 3DCRT to reduce adverse GI effects of radiotherapy

Patient or population: People with urological (prostate) and gynaecological (cervical) cancer
Settings: Tertiary care setting
Intervention: IMRT
Comparison: 3DCRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	3DCRT	IMRT				
Mean GI symptom scores (EORTC-QLQPR25 scale; lower scores better)	At 6 months post-RT, the mean GI symptom score in the control group was 9	At 6 months post-RT, the mean GI symptom score in the intervention group was 4 (1 to 9 points lower)	**MD -5.00** (-9.06 to -0.94)	181 (1)	⊕⊕◯◯ **low**[1,2]	-
Acute and late GI toxicity Grade 2+	Acute toxicity (up to 3 months post-RT): **445 per 1000**	Acute toxicity (up to 3 months post-RT): **214 per 1000** (116 to 392)	**RR 0.48** (0.26 to 0.88)	444 (4)	⊕⊕◯◯ **low**[1,3]	Inconsistency was present between studies in the gynaecological cancer subgroup but not between gynaecological and urological subgroups
	Late toxicity (from 6 months post-RT): **228 per 1000**	Late toxicity (from 6 months post-RT): **84 per 1000** (48 to 148)	**RR 0.37** (0.21 to 0.65)	332 (2)	⊕⊕◯◯ **low**[4]	Findings were consistent across gynaecological and urological subgroups

Diarrhoea (grade 2+)	Acute toxicity (up to 3 months post-RT): 720 per 1000	Acute toxicity (up to 3 months after RT): **273 per 1000** (158 to 490)	**RR 0.38** (0.22 to 0.68)	72 (1)	⊕⊕◯◯ **low**[1,5]	-
QoL scores	-	-	Not estimable	0	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **MD:** mean difference; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level for design limitations (unclear risk of bias).
[2]Downgraded for imprecision (evidence based on continuous data from one study of 181 participants).
[3]Downgraded for inconsistency across studies (I^2 = 77%).
[4]Downgraded two levels for design limitations as the analysis includes data from Viani 2016 (51.8% weight), which were imputed from percentages and considered at high risk of bias for this outcome, and one study considered to have an unclear risk of bias.
[5]Downgraded one level for imprecision (evidence is based on 71 participants from one small study).

BT compared with EBRT to reduce adverse GI effects of radiotherapy

Patient or population: People with urological (prostate) and gynaecological (endometrial) cancer
Settings: Tertiary care settings
Intervention: BT
Comparison: EBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	EBRT	BT				
Mean GI symptom scores	-	-	Not estimable	348 (1)	-	1 high-quality study reported data on GI symptom scores at various time points after radiotherapy up to 5 years. Due to the numberous time points and domains, we could not use these data in the review meta-analysis in a meaningful way. However, the findings favoured BT for 'limitation in daily activities due to bowel symptoms' ($P < 0.001$), faecal leakage ($P < 0.001$) and rectal blood loss ($P = 0.04$) at most time points up to 5 years post-radiotherapy

Acute and late GI toxicity (grade 2+)	Acute GI toxicity (Up to 3 months after RT): -	Acute GI toxicity (Up to 3 months after RT): -	not pooled	not pooled	-	Due to clinical and statistical heterogeneity, data from the two relevant studies were not pooled for this outcome and subgroup evidence was graded separately. Evidence from the urological (prostate) cancer was graded as very low certainty. However, the evidence in favour of BT from the one study in the 'gynaecological cancer' subgroup was graded as high-certainty (RR 0.02, 95%CI 0.00 to 0.18; participants = 423; studies = 1)
	Late GI toxicity (from 6 months post-RT): **per 1000**	Late GI toxicity (from 6 months post-RT): **per 1000** (48 to 148)	**RR 0.16** **(**0.02 to 1.33)	423 (1)	⊕⊕◯◯ **low**[3]	-
Diarrhoea (grade 2+)	Acute diarrhoea (Up to 3 months after RT)	-	Not estimable	0	-	No data
QoL scores (EORTC Q30)	Measured in one study at various time points up to 5 years and beyond	-	Not estimable	348 (1)	-	1 high-quality study reported data on QoL scores at various time points after radiotherapy to 5 years and found no clear differ-

			ence in global health status between BT and EBRT groups

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded for inconsistency (I^2 = 74%).
[2]Downgraded -1 for imprecision.
[3]Downgraded -2 for imprecision (wide CI crossing the line of no effect and few events).

Reduced radiation dose volume compared with standard dose volume to reduce adverse GI effects of radiotherapy

Patients/population: People undergoing RT for pelvic cancer[1]
Settings: Tertiary care
Intervention: Reduced radiation dose-volume
Comparison: Standard radiation dose-volume

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	standard radiation dose volume	reduced radiation dose volume				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (up to 3 months post-RT) : 282 per 1000	Acute (up to 3 months post-RT): 341 per 1000 (228 to 510)	**RR 1.21** (0.81 to 1.81)	211 (1)	⊕⊕⊕◯ **moderate**[2]	-
	Late (1 year post-RT): 37 per 1000	Late (1 year post RT): 38 per 1000 (6 to 258)	**RR 1.02** (0.15 to 6.97)	107 (1)	⊕⊕◯◯ **low**[3]	-
	Late (2 years post-RT): 71 per 1000	Late (2 years post RT): 27 per 1000 (3 to 247)	**RR 0.38** (0.04 to 3.48)	79 (1)	⊕⊕◯◯ **low**[3]	-
Diarrhoea (grade 2+)	-	-	not estimable	-	-	No data
QOL scores	-	-	not estimable	-	-	no data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]All evidence in the SOF was derived from participants undergoing treatment for bladder cancer.
[2]Downgraded due to imprecision (wide CI crossing the line of no effect).
[3]Downgraded -2 due to imprecision (wide CI and very few events).

Higher bladder volume (BV) compared with lower BV preparation to reduce adverse GI effects of radiotherapy

Patients/population: Men undergoing RT for prostate cancer
Settings: Tertiary care
Intervention: BV prep of 1080 mls
Comparison: BV prep of 540 mls

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	540 mls BV prep	1080 mls BV prep				
Mean GI symptom scores (during RT)	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (up to 3 months post RT): 60 per 1000	Acute (up to 3 months post-RT): 133 per 1000 (37 to 476)	**RR 2.22** (0.62 to 7.93)	110 (1)	⊕⊕◯◯ **low**[1,2]	-
	Late (up to 1 year post-RT): 158 per 1000	Late (up to 1 year post-RT): 70 per 1000 (19 to 261)	**RR 0.44** (0.12 to 1.65)	81 (1)	⊕⊕◯◯ **low**[1,2]	-
Diarrhoea (grade 2+)	-	-	not estimable	-	-	No data
QOL scores	-	-	not estimable	-	-	Insufficient data for meta-analysis; however, authors stated that "There were no statistically significant associations between bladder filling preparations...and me-

				dian QOL scores.''

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded due to imprecision (wide CI crossing the line of no effect).
[2]Downgraded for study design limitations (only study judged to have unclear risk of bias).

Evening RT compared with morning RT to reduce adverse GI effects of radiotherapy

Patients/population: Women undergoing RT for cervical cancer
Settings: Tertiary care
Intervention: Evening RT
Comparison: Morning RT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	morning RT	evening RT				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (during RT): 349 per 1000	Acute (during RT): 178 per 1000 (119 to 265)	**RR 0.51** (0.34 to 0.76)	294 (2)	⊕⊕◯◯ **low**[1]	Measured as diarrhoea grade 2+
	Late: -	Late: -	not estimable	-	-	No data
Diarrhoea (grade 2+) (during RT)	See evidence on acute toxicity (grade 2+)					-
QOL scores	-	-	not estimable	-	-	no data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded for study design limitations (most weight derived from one study assessed as having a high risk of bias).

Transperineal hydrogel spacer/injection compared with no intervention to reduce adverse GI effects of radiotherapy

Patients/population: Men undergoing RT for prostate cancer
Settings: Tertiary care
Intervention: Transperineal hydrogel spacer/injection
Comparison: No intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no intervention	hydrogel spacer				
Mean GI symptom scores	-	-	not estimable	-	-	No data available
Acute and late GI toxicity (grade 2+)	Acute (up to 3 months post-RT): 65 per 1000	Acute (up to 3 months post-RT): 33 per 1000 (5 to 220)	**RR 0.51** (0.08 to 3.38)	289 (2)	⊕⊕◯◯ **low**[1,2]	Events in these contributing studies were few
	Late (up to 15 months post-RT): 14 per 1000	Late (up to 15 months post-RT): 2 per 1000 (0 to 55)	**RR 0.16** (0.01 to 3.96)	220 (1)	⊕⊕◯◯ **low**[1,2]	Events in this contributing study were few
	Late (median of 3 years): 67 per 1000	Late (median of 3 years): 15 per 1000 (0 to 88)	**RR 0.07** (0.00 to 1.31)	139 (1)	⊕⊕◯◯ **low**[1,2]	Events in this contributing study were few
Diarrhoea (grade 2+)	-	-	not estimable	-	-	No data available
QOL scores	-	-	not estimable	-	-	Data could not be meta-analysed, but findings from 2 studies suggested beneficial effects on bowel-related

			QOL with the hydrogel spacer (see Effects of interventions section).

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded for study design limitations (contributing study judged to have unclear risk of bias).
[2]Downgraded for imprecision (very few events and wide CI crossing the line of no effect).

Endorectal balloon compared with no intervention to reduce adverse GI effects of radiotherapy

Patients/population: Men undergoing RT for prostate cancer
Settings: Tertiary care
Intervention: Endorectal balloon
Comparison: No intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no intervention	endorectal balloon				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (during RT): 292 per 1000	Acute (during RT): 292 per 1000 (120 to 707)	**RR 1.00** (0.41 to 2.42)	48 (1)	⊕◯◯◯ **very low**[1,2]	Evidence on acute grade 1+ GI toxicity was of low certainty and suggested little or no difference in acute toxicity with ERB (see Effects of interventions section)
	Late (up to 1 year): 83 per 1000	Late (up to 1 year): 17 per 1000 (1 to 329)	**RR 0.20** (0.01 to 3.96)	48 (1)	⊕◯◯◯ **very low**[1,2]	Evidence on late grade 1+ toxicity was of low certainty and suggested a reduction in late toxicity with ERB (see Effects of interventions section)
Diarrhoea (grade 2+)	Late (2 to 4 years): 565 per 1000	Late (2 to 4 years): 401 per 1000 (209 to 723)	**RR 0.71** (0.37 to 1.35)	43 (1)	⊕◯◯◯ **very low**[1,2]	-

QOL scores	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QOL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded for study design limitations (contributing study judged to have unclear risk of bias).
[2]Downgraded two levels for imprecision (few events and wide CI crossing the line of no effect).

Aminosalicylates compared with placebo administered prophylactically to reduce adverse GI effects of radiotherapy

Patient or population: People undergoing pelvic radiotherapy for urological, gynaecological or colorectal cancer
Settings: Tertiary care
Intervention: Aminosalicylates
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	aminosalicylates				
Mean GI symptom scores (IBDQ-B)	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (during treatment) (mesalazine): 380 per 1000	Acute (during treatment) (mesalazine): 388 (464 to 551)	**RR 1.02** (1.22 to 1.45)	143 (2)	⊕⊕⊕◯ **moderate**[1]	Formulations appear to differ in effects on this outcome; therefore subgroup data were not pooled. The sulfasalazine findings were very inconsistent (I^2 = 73%) across the 2 contributing studies, with the better-quality study showing no re-
	Acute (during treatment) (sulphasalazine): 447 per 1000	Acute (during treatment) (sulphasalazine): 130 (49 to 335)	**RR 0.29** (0.11 to 0.75)	182 (2)	⊕⊕◯◯ **low**[1,2]	
	Late: -	Late: -	not estimable	-	-	No data
Diarrhoea (grade 2+)	-	-	not pooled	-	-	As above, subgroup data were not pooled and findings were as follows:

						• mesalazine: RR 1.55, 95% CI 1.14 to 2.10; participants = 191;
QOL scores	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded for study design limitations (analysis included studies at an unclear risk of bias).
[2]Downgraded for inconsistency across studies (I^2 > 60%).

itations (unclear risk of bias) in all subgroups, and also due to inconsistency for the sulfasalazine subgroup

Superoxide dismutase compared with no intervention to reduce adverse GI effects of radiotherapy

Patient or population: People with rectal cancer
Settings: Tertiary care
Intervention: Superoxide dismutase (IM)
Comparison: No intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no intervention	superoxide dismutase				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (3 months): 217 per 1000	Acute (3 months): 43 per 1000 (11 to 187)	**RR 0.20** (0.05 to 0.86)	92 (1)	⊕⊕◯◯ **low**[1,2]	-
	Late: (1 year): 135 per 1000	Late (1 year): 12 per 1000 (1 to 209)	**RR 0.09** (0.01 to 1.55)	75 (1)	⊕◯◯◯ **very low**[1,3]	-
	Late (2 to 4 years): 193 per 1000	Late (2 to 4 years): 12 per 1000 (0 to 225)	**RR 0.06** (0.00 to 1.11)	68 (1)	⊕◯◯◯ **very low**[1,3]	-
Diarrhoea (grade 2+)	-	-	not estimable	-	-	No data
QOL scores	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded due to design limitations (study assessed as unclear risk of bias as it lacked methodological details).
[2]Downgraded due to imprecision (only one small study of 92 participants contributed data).
[3]Downgraded -2 due to imprecision (few events and wide CI crossing the line of no effect).

Corticosteroid enema compared with placebo to reduce adverse GI effects of radiotherapy

Patients/population: Men with prostate cancer
Settings: Tertiary care
Intervention: Corticosteroid enema
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	corticosteroid enema				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (3 months): 619 per 1000	Acute (3 months): 526 per 1000 (384 to 712)	**RR 0.85** (0.62 to 1.15)	126 (1)	⊕◯◯◯ **very low**[1,2,3]	-
	Late: (1 year): 136 per 1000	Late (1 year): 91 per 1000 (31 to 262)	**RR 0.67** (0.23 to 1.93)	114 (1)	⊕⊕◯◯ **low**[4]	-
Diarrhoea (grade 2+)	Acute: -	Acute: -	not estimable	-	-	No data
	Late (1 year): 68 per 1000	Late (1 year): 73 per 1000 (19 to 277)	**RR 1.07** (0.28 to 4.08)	114 (1)	⊕⊕◯◯ **low**[4]	-
QOL scores	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded due to design limitations (study assessed as unclear risk of bias as it lacked methodological details).
[2]Downgraded due to indirectness (comparison group in this study was sucralfate not placebo).
[3]Downgraded due to imprecision (wide CI crossing the line of no effect).
[4]Downgraded -2 due to imprecision (few events and wide CI crossing the line of no effect).

Sucralfate compared with placebo administered prophylactically to reduce adverse GI effects of radiotherapy

Patient or population: People undergoing pelvic radiotherapy for urological, gynaecological or colorectal cancer
Settings: Tertiary care
Intervention: Sucralfate
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	sucralfate				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+) [acute = during RT; late = 6 months post-RT]	Acute (oral route): 398 per 1000	Acute (oral route): 426 per 1000 (330 to 553)	**RR 1.07** (0.83 to 1.39)	335 (1)	⊕⊕⊕◯ **moderate**[1]	-
	Acute (rectal route): 524 per 1000	Acute (rectal route): 618 per 1000 (456 to 838)	**RR 1.18** (0.87 to 1.60)	126 (1)	⊕⊕◯◯ **low**[1,2]	-
	Late (oral route): 284 per 1000	Late (oral route): 216 per 1000 (110 to 324)	**RR 0.76** (0.51 to 1.14)	298 (1)	⊕⊕⊕◯ **moderate**[1]	No data on rectal route
Diarrhoea (grade 2+) [during RT]	Acute (oral route): 490 per 1000	Acute (oral route): 397 per 1000 (201 to 794)	**RR 0.81** (0.41 to 1.62	)284 (4)	⊕⊕◯◯ **low**[1,3]	-
	Acute (rectal route): 357 per 1000	Acute (rectal route): 293 per 1000 (143 to 546)	**RR 0.82** (0.44 to 1.53)	83 (1)	⊕◯◯◯ **very low**[1,2,4]	-

QOL scores	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded for imprecision (wide CI crossing the line of no effect).
[2]Downgraded for design limitations.
[3]Downgraded for inconsistency (I^2 = 82%).
[4]Small sample, few events (imprecision).

Amifostine compared with no intervention to reduce adverse GI effects of radiotherapy

Patient or population: People with urological, gynaecological or colorectal cancer
Settings: Tertiary care
Intervention: Amifostine (subcutaneous or intravenously administered)
Comparison: No intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no intervention	amifostine				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (during RT): 398 per 1000	Acute (during RT: **100 per 1000** (60 to 167)	**RR 0.25** 0.15 to 0.42	278 (3)	⊕⊕◯◯ **low**[1]	-
	Acute (up to 3 months): 174 per 1000	Acute (up to 3 months): 21 per 1000 (2 to 369)	**RR 0.12** (0.01 to 2.12)	44 (1)	⊕◯◯◯ **very low**[2,3,4]	-
	Late (up to 1 year): 59 per 1000	Late (up to 1 year): 87 per 1000 (38 to 204)	**RR 1.48** (0.64 to 3.45)	249 (2)	⊕⊕◯◯ **low**[2,4]	-
Diarrhoea (grade 2+) during treatment	Acute (during RT): 500 per 1000	Acute (during RT):**125 per 1000** (30 to 490)	**RR 0.25** (0.06 to 0.98)	36 (1)	⊕◯◯◯ **very low**[2,3,4]	-
QOL scores	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded twice due to design limitations (two studies that contribute >95% of the weight in the meta-analysis were assessed as high risk of bias).
[2]Downgraded due to imprecision (wide CI crossing the line of no effect).
[3]Small sample size.
[4]Downgraded due to design limitations (unclear risk of bias).

Sodium butyrate compared with placebo to reduce adverse GI effects of radiotherapy

Patients/population: Men undergoing RT for prostate cancer
Settings: Tertiary care
Intervention: Sodium butyrate enema
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	sodium butyrate enema (2 g daily)				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (during RT): 179 per 1000	Acute (during RT): 163 per 1000 (74 to 354)	**RR 0.91** (0.41 to 1.98)	79 (1)	⊕⊕⊕◯ **moderate**[1]	-
	-	-	not estimable	-	-	No data
Diarrhoea (grade 2+)	-	-	not estimable	-	-	No data
QOL scores	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded due to imprecision (wide CI crossing the line of no effect). We did not downgrade twice for imprecision as this evidence was from a good study evaluating three different doses of sodium butyrate (only the 2 g dose is represented here) and none of the doses showed a clear difference in effect.

Selenium compared with placebo to reduce adverse GI effects of radiotherapy

Patients/population: Women undergoing RT for gynecological cancer
Settings: Tertiary care
Intervention: Oral selenium
Comparison: No intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	oral selenium				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute: -	-	not estimable	-	-	No data
	Late: -	-	not estimable	-	-	No data
Diarrhoea (grade 2+)	Acute (during RT): 190 per 1000	Acute (during RT): 76 per 1000 (23 to 268)	**RR 0.40** 0.12 to 1.41	81 (1)	⊕⊕◯◯ **low**[1,2]	-
QOL scores	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded due to design limitations (both studies at unclear risk of bias).
[2]Downgraded due to imprecision (wide CI crossing the line of no effect).

Bile acid sequestrants compared with placebo to reduce adverse GI effects of radiotherapy

Patients/population: People with pelvic cancer
Settings: Tertiary care
Intervention: Bile acid sequestrants
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	bile acid sequestrants				
Mean GI symptom scores (during RT)	The mean (diarrhoea) score in the single study evaluating this outcome was 1.5	Corresponding mean score of 2 (1.5 to 2.5)	**MD 0.50** (-0.00 to 1.00)	33 (1)	⊕◯◯◯ **very low**[1,2]	-
Acute and late GI toxicity (grade 2+)	Acute (during RT): 125 per 1000	Acute (during RT): 530 per 1000 (134 to 1000)	**RR 4.24** (1.07 to 16.70)	33 (1)	⊕⊕◯◯ **low**[1,3]	Findings suggest potential for harm
	-	-	not estimable	-	-	No data
Diarrhoea (grade 2+)	Acute (during RT: 125 per 1000	Acute (during RT): 353 per 1000 (83 to 1000)	**RR 2.82** (0.66 to 12.01)	33 (1)	⊕◯◯◯ **very low**[1,2]	-
QOL scores	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded due to design limitations (study had unclear risk of bias overall and unvalidated diarrhoea symptom scale was used for this outcome).
[2]Downgraded twice due to imprecision (small sample size and wide CI crossing the line of no effect).
[3]Downgraded one level due to imprecision (small sample size).

Misoprostol compared with placebo to reduce adverse GI effects of radiotherapy

Patients/population: Men with prostate cancer
Settings: Tertiary care
Intervention: Misoprostol suppository
Comparison: Placebo

Outcomes[1]	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	misoprostol suppository				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (during RT): 217 per 1000	Acute (during RT): 340 per 1000 (165 to 545)	**RR 1.38** (0.76 to 2.51)	100 (1)	⊕⊕◯◯ **low**[2,3]	See footnote 1 below
	Late: -	Late: -	not estimable	-	-	No data
Diarrhoea (grade 2+)	Acute (during RT): 217 per 1000	Acute (during RT): 217 per 1000 (100 to 475)	**RR 1.00** (0.46 to 2.19)	100 (1)	⊕◯◯◯ **very low**[2,3,4]	Late effects on diarrhoea at 1+ years post-RT were also reported in this single study and the evidence was also of a very low certainty, mainly due to few events
QOL scores	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Also see Effects of interventions section for findings on rectal bleeding, which suggest the potential for harm with this intervention.
[2]Downgraded due to design limitations (unclear risk of bias).
[3]Downgraded due to imprecision (wide CI crossing the line of no effect).
[4]Downgraded due to few events.

Magnsium oxide compared with placebo to reduce adverse GI effects of radiotherapy

Patients/population: Men with prostate cancer
Settings: Tertiary care
Intervention: Oral magnesium oxide
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	magnesium oxide				
Mean GI symptom scores (during RT)	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (during RT): 217 per 1000	Acute (during RT): 369 per 1000 (189 to 718)	**RR 1.70** (0.87 to 3.31)	92 (1)	⊕⊕⊕◯ **moderate**[1]	Findings indicate potential for harm
	-	-	not estimable	-	-	No data
Diarrhoea (grade 2+)	-	-	not estimable	-	-	No data
QOL scores	-	-	not estimable	-	-	No data for meta-analysis. The only included study presents these data graphically and concludes that there was "a trend to worsened quality of life" in the magnesium oxide arm

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded due to imprecision (wide CI crossing the line of no effect).

Octreotide compared with placebo to reduce adverse GI effects of radiotherapy

Patients/population: People undergoing RT for pelvic cancer
Settings: Tertiary care
Intervention: Octreotide injection
Comparison: Placebo

Outcomes[1]	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	octreotide injection				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute: -	-	not estimable	-	-	No data
	Late: -	-	not estimable	-	-	No data
Diarrhoea (grade 2+)	Acute (during RT): 491 per 1000	Acute (during RT): 496 per 1000 (373 to 663)	**RR 1.01** (0.76 to 1.35)	340 (2)	⊕⊕⊕◯ **moderate**[2]	-
QOL scores	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Also see Effects of interventions section for findings on rectal bleeding, which suggest the potential for harm with this intervention.

[2]Downgraded due to design limitations (both studies at unclear risk of bias).

Diet interventions compared with usual practice to reduce adverse GI effects of radiotherapy

Patient or population: People undergoing pelvic radiotherapy for urological, gynaecological or colorectal cancer
Settings: Tertiary care
Intervention: Dietary intervention
Comparison: Control (usual on-treatment diet)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk control	Corresponding risk diet				
Elemental diet						
Mean GI symptom scores (IBDQ-B) (higher scores better)	Acute (during RT): median score 60 (35 - 69) Acute effect (3 months post RT): median score 69 (34 - 70)	Acute (during RT): median score 57 (23-66) Acute effect (3 months post-RT): median score 68 (42 - 70)	not estimable	50 (1)	⊕⊕◯◯ **low**[1]	There was poor compliance in this study and only a third of daily calories substituted with elemental diet
Acute and late GI toxicity (grade 2+)	Acute: -	Acute: -	not estimable	-	-	No data
	Late: -	Late: -	not estimable	-	-	No data
Diarrhoea (grade 2+)	Acute (during RT): 560 per 1000	Acute (during RT): 442 per 1000 (252 to 773)	**RR 0.79** (0.45 to 1.38)	50 (1)	⊕⊕◯◯ **low**[2]	-
QOL scores (IBDQ) (higher scores better)	During RT the mean QOL score in the control group was 186.4	During RT the mean QOL score in the diet group 4.6 points higher	**MD 4.60** (-12.40 to 21.60)	50 (1)	⊕⊕◯◯ **low**[1]	-

		(12.4 points lower to 21.6 points higher)				
Lactose-restricted diet						
Mean GI symptom scores (IBDQ-B) (higher scores better)	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute: -	Acute: -	not estimable	-	-	No data
	Late: -	Late: -	not estimable	-	-	No data
Diarrhoea (grade 1+)	Acute (during RT): 397 per 1000	Acute (during RT): 294 per 1000 (179 to 488)	**RR 0.74** (0.45 to 1.23)	119 (1)	⊕⊕◯◯ **low**[3]	This study intervention included low insoluble fibre. No grade 2+ events occurred
QOL scores (QLQ-PR25)	-	-	not estimable	119 (1)	-	In 1 study, QOL was reported for many time points and domains up to 24 months post-RT and study authors found little difference between study arms at any time point evaluated; however, these data could not be extracted and analysed for review purposes in a meaningful way
High-fibre diet						

Mean GI symptom scores (IBDQ-B) (higher scores better)	Acute (at end of RT): The mean IBDQ-B score in the control group was 48.7	Acute: At the end of RT, the mean IBDQ-B score in the diet group was 2. 80 points higher (from 1.81 points lower to 7. 41 points higher)	**MD 2.80** (-1.81 to 7.41)	108 (1)	⊕⊕◯◯ **low**[4]	Mean change in GI symptom scores from baseline to end of RT was also reported in 1 study (Wedlake 2017) and the evidence suggests that the change in IBDQ-B scores from baseline may be reduced with a high-fibre diet (see Results section)
	Late (at 1 year post-RT) : At 1 year post-RT, the mean IBDQ-B score was 55.7	At 1 year post-RT, the mean IBDQ-B score in the diet group was 6. 1 points higher (1.71 to 10.49 points higher)	**MD 6.10** (1.71 to 10.49)	108 (1)	⊕⊕◯◯ **low**[4]	As above, findings on mean change in GI symptom scores from 1 study suggests that IBDQ-B scores are less likely to be reduced at 1 year post-RT from baseline with a high-fibre diet than with a usual diet (see Results section)
Acute and late GI toxicity (grade 2+)	-	-	not estimable	-	-	No data
Diarrhoea (grade 2+)	Acute (during RT): 540 per 1000	Acute (during RT): 351 per 1000 (205 to 594)	**RR 0.65** (0.38 to 1.10; participants)	74 (2)	⊕⊕◯◯ **low**[4]	-
QOL scores (IBDQ) (higher scores better)	During RT the mean QOL score in the control group was 162	During RT, the mean QOL score in the diet group was 6.5 points higher (6 lower to 19	**MD 6.50** (-5.88 to 18.88)	108 (1)	⊕⊕◯◯ **low**[4]	-

		higher)				
	At 1 year post-RT the mean QOL score was 173	At 1 year post-RT, the mean QOL score in the diet group was 20.5 points higher (10 to 31 higher)	**MD 20.50** (9.97 to 31.03)	108 (1)	⊕⊕◯◯ **low**[5]	-
Low-fibre diet						
Mean GI symptom scores (IBDQ-B) (higher scores better)	Acute (at end of RT): The mean IBDQ-B score in the control group was 48.7	At the end of RT, the mean IBDQ-B score in the diet group was 3.5 points higher (from 0. 93 points lower to 7.93 points higher)	**MD 3.50** (-0.93 to 7.93)	107 (1)	⊕⊕◯◯ **low**[4]	Mean change in GI symptom scores from baseline to end of RT was also reported in 1 study (Wedlake 2017) and findings suggest that there may be little or no difference between diet and control groups (see Results section)
	Late (at 1 year post RT) : At 1 year post RT, the mean IBDQ-B score was 55.7	At 1 year post-RT, the mean IBDQ-B score in the diet group was 3.30 points higher (from 0. 94 points lower to 7.54 points higher)	**MD 3.30** (-0.94 to 7.54)	107 (1)	⊕⊕◯◯ **low**[4]	As above, mean change in GI symptom scores from baseline to 1 year post-RT was also reported in one study (Wedlake 2017) and findings suggest that there may be little or no difference between diet and control groups (see Results section)
Acute and late GI toxicity (grade 2+)	-	-	not estimable	-	-	No data

Diarrhoea (grade 1+)	Acute (during RT): 397 per 1000	Acute (during RT): 294 per 1000 (179 to 488)	**RR 0.74** (0.45 to 1.23)	119 (1)	⊕⊕◯◯ **low**[2]	This study intervention included lactose-restriction
QOL scores (IBDQ) (higher scores better)	Acute (during RT): During RT the mean QOL score in the control group was 161.5	Acute (during RT): During RT, the mean QOL score in the diet group was 9.80 points higher (1.91 lower to 21.51 points higher)	**MD 9.80** (-1.91 to 21.51)	107 (1)	⊕⊕◯◯ **low**[4]	-
	Late (1 year post-RT): At 6 months post-RT, the mean QOL score in the control group was 173.6	Late: At 1 year post-RT, the mean QOL score in the diet group was 9.4 points higher (1.78 lower to 20.58 points higher)	**MD 9.40** (-1.78 to 20.58)	107 (1)	⊕⊕◯◯ **low**[4]	-
Low-fat diet						
Mean GI symptom scores (Vaizey scale) (higher scores better)	Acute: During RT the mean GI symptom score in the control group was 4.6	Acute: During RT, the mean GI symptom score in the diet group was 4.4 (2.4 to 6.5)	**MD -0.20** (-2.29 to 1.89)	70 (1)	⊕⊕◯◯ **low**[4]	-
Acute and late GI toxicity (grade 2+)	436 per 1000	50 per 1000 (310 to 802)	**RR 1.15** (0.71 to 1.84)	79 (1)	⊕⊕◯◯ **low**[4]	-
Diarrhoea	-	-	not estimable	-	-	No data
QOL scores (IBDQ)	During RT the mean QOL score in the control group was 187	During RT, the mean QOL score in the diet group was 189 (177 to 201)	**MD 2.40** (-9.52 to 14.32)	76 (1)	⊕⊕◯◯ **low**[4]	-

Prebiotic diet						
Mean GI symptom scores (IBDQ-B) (higher scores better)	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	-	-	not estimable	-	-	No data
Diarrhoea	-	-	not estimable	-	-	No data
QOL scores (IBDQ)	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **MD:** Mean Difference; **QoL**: quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded -1 for design limitations (risk of bias due to poor compliance) and -1 for indirectness (intervention involved substituting a third of calories instead of 100%, which might have a different effect on outcomes).
[2]Downgraded -1 for design limitations (risk of bias) and -1 imprecision (wide CI crosses the line of no effect).
[3]Downgraded -1 for indirectness (dietary intervention involved both lactose-restriction and low insoluble fibre) and -1 for imprecision (wide CI crosses the line of no effect).
[4]Downgraded for design limitations and imprecision.
[5]Downgraded -2 for design limitations (no assessor blinding for this outcome and potential risk of performance bias).

Protein supplements compared with no intervention to reduce adverse GI effects of radiotherapy

Patients/population: Individuals undergoing RT for pelvic cancer
Settings: Tertiary care
Intervention: Protein supplements
Comparison: No intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no intervention	protein supplements				
Mean GI symptom scores (lower is better)	-	-	not estimable	-	-	Data were insufficient for meta-analysis. However, diarrhoea scores significantly deteriorated from baseline to end of RT in both the protein supplement and the control groups, and mean diarrhoea scores (without standard deviations) were similar at 3-month follow-up
Acute and late GI toxicity (grade 2+)	Acute: -	Acute: -	not estimable	-	-	See evidence on diarrhoea
	Late: -	Late: -	not estimable	-	-	See evidence on diarrhoea
Diarrhoea (grade 2+)	Acute (end of RT): 459 per 1000	Acute (end of RT): 243 per 1000 (124 to 473)	**RR 0.53** (0.27 to 1.03)	74 (1)	⊕◯◯◯ **very low**[1,2,3]	-

	Acute (3 months post-RT): 351 per 1000	Acute (3 months post-RT): 14 per 1000 (0 to 211)	**RR 0.23** (0.07 to 0.74)	74 (1)	⊕⊕◯◯ **low**[2,3]	-
	Late (5 years post-RT): 296 per 1000	Late (5 years post-RT): 15 per 1000 (0 to 231)	**RR 0.60** (0.23 to 1.51)	61 (1)	⊕◯◯◯ **very low**[1,2,3]	-
QOL scores	-	-	not estimable	-	-	Data were insufficient for meta-analysis. However, mean global QOL scores (without standard deviations) were reported to be significantly different (better) compared with baseline scores in the protein supplement group at the end or RT and at 3 months post-RT, but were significantly worse than baseline scores at these time points in the control group

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QOL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded due to design limitations (control group received no intervention).

[2]Downgraded due to imprecision (small study with few events).
[3]Downgraded due to imprecision (wide CI crossing the line of no effect).

Probiotics compared with no probiotics to reduce adverse GI effects of radiotherapy

Patients/population: People undergoing RT for pelvic cancer
Settings: Tertiary care
Intervention: probiotics
Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo or no intervention	probiotics				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute: -	Acute: -	not estimable	-	-	No data
	Late: -	Late: -	not estimable	-	-	No data
Diarrhoea (grade 2+)	Acute (during RT): 440 per 1000	Acute (during RT): 194 per 1000 (92 to 414)	**RR 0.43** (0.22 to 0.82)	923 (5)	⊕⊕◯◯ **low**[1,2]	
QOL scores	-	-	not estimable	-	-	Very limited narrative data available; see Effects of interventions section.

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio **QOL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded due to design limitations (4 studies assessed as having unclear risk of bias, and one study assessed as having high risk of bias overall).
[2]Downgraded due to inconsistency (I^2 = 91%).

Proteolytic enzymes compared with control to reduce adverse GI effects of radiotherapy

Patients/population: People undergoing RT for pelvic cancer
Settings: Tertiary care
Intervention: Proteolytic enzymes
Comparison: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo or no intervention	proteolytic enzymes				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (3 months post-RT): 367 per 1000	Acute (3 months post RT): 165 per 1000 (88 to 323)	**RR 0.45** (0.24 to 0.88)	120 (1)	⊕⊕◯◯ **low**[1]	When grade 1 data were included, the evidence suggested that there may be little or no difference in acute toxicity
	Late: -	Late: -	not estimable	-	-	No data
Diarrhoea (grade 2+)	Acute (during RT): 357 per 1000	Acute (during RT): 571 per 1000 (317 to 1000)	**RR 1.60** (0.89 to 2.89)	56 (1)	⊕◯◯◯ **very low**[1,2]	This study also reported that more participants in the proteolytic enzyme group required medication for diarrhoea symptom control (see Effects of interventions section)
QOL scores	-	-	not estimable	-	-	No data

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio **QOL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded -2 due to design limitations (only one contributing study assessed as having high risk of bias).
[2]Downgraded due to imprecision (one small study and CI crossing the line of no effect).

Glutamine compared with placebo to reduce adverse GI effects of radiotherapy

Patients/population: People undergoing RT for pelvic cancer
Settings: Tertiary care
Intervention: Oral glutamine
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	glutamine				
Mean GI symptom scores	-	-	not estimable	-	-	No data
Acute and late GI toxicity (grade 2+)	Acute (during RT): 86 per 1000	Acute (during RT): 206 per 1000 (58 to 734)	**RR 2.40** (0.68 to 8.53)	69 (1)	⊕⊕◯◯ **low**[1]	-
	Late (1 year): 74 per 1000	Late (1 year): 334 per 1000 (17 to 1000)	**RR 4.52** (0.23 to 90.08)	57 (1)	⊕⊕◯◯ **low**[1]	-
Diarrhoea (grade 2+)	Acute (during RT): 500 per 1000	Acute (during RT): 495 per 1000 (395 to 625)	**RR 0.98** (0.78 to 1.24)	289 (4)	⊕⊕⊕⊕ **high**	We did not downgrade this evidence for design limitations as the findings of the studies with unclear risk of bias were consistent with the low risk of bias study and did not show benefit in favour of the intervention

QOL scores	-	-	not estimable	-	-	1 study reported that median QOL scores were similar for glutamine and placebo groups at 12 months and 24 months; however these data were not in a usable form for meta-analysis

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **QOL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded -2 for imprecision (small study with few events, and wide CI crossing the line of no effect).

Counselling compared with no intervention to reduce adverse GI effects of radiotherapy

Patients/population: Individuals undergoing RT for pelvic cancer
Settings: Tertiary care
Intervention: Dietary or other counselling
Comparison: No intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality/certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no intervention	counselling				
Mean GI symptom scores (lower is better)	At 3 months post-RT, the mean GI symptom score (diarrhoea) in the control group was 1.6	At 3 months post-RT, the mean GI symptom score (diarrhoea) in the control group was 1.68 (1.22 to 2.14)	**MD 0.08** (-0.38 to 0.54)	152 (1)	⊕⊕◯◯ **low**[1,2]	-
Acute and late GI toxicity (grade 2+)	Acute: -	Acute: -	not estimable	-	-	See evidence on diarrhoea
	Late: -	Late: -	not estimable	-	-	See evidence on diarrhoea
Diarrhoea (grade 2+)	Acute (end of RT): 459 per 1000	55 per 1000 (14 to 165)	**RR 0.12** (0.03 to 0.47)	74 (1)	⊕⊕◯◯ **low**[2,3]	-
	Acute (3 months post-RT): 351 per 1000	14 per 1000 (0 to 211)	**RR 0.04** (0.00 to 0.60)	74 (1)	⊕⊕◯◯ **low**[2,3]	-
	Late (5 years post-RT): 296 per 1000	15 per 1000 (0 to 231)	**RR 0.05** (0.00 to 0.78)	61 (1)	⊕⊕◯◯ **low**[2,3]	-

QOL scores (5-point VAS; lower is better)	At 3 months post-RT, the mean QOL (fatigue) score in the control group was 2.17	At 3 months post-RT, the mean QOL (fatigue) score in the control group was 1.76 (1.37 to 2.18)	**MD -0.41** (-0.83 to 0.01)	152 (1)	⊕○○○ **very low**[1,2,4]	In another included study with no usable data for meta-analysis, authors reported that, "at 3 months GI [counselling group] patients maintained/improved function, symptoms and single-item scores (P<0.02)" compared with baseline scores, whereas "QOL remained as poor as after radiotherapy" in the control group
	At 3 months post RT, the mean QOL (sleeping problem) score in the control group was 1.04	At 3 months post RT, the mean QOL (sleeping problem) score in the control group was 0.58 (0.15 to 1.01)	**MD -0.46** (-0.89 to -0.03)	152 (1)	⊕⊕○○ **low**[1,2]	

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **MD:** mean difference; **QOL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded due to imprecision (small study; continuous data).
[2]Downgraded due to design limitations (control group received no intervention).
[3]Downgraded due to imprecision (small study with few events).
[4]Downgraded due to imprecision (wide CI crossing the line of no effect).

DISCUSSION

Summary of main results

The review included 92 studies involving more than 10,000 participants and 44 different interventions to reduce adverse gastrointestinal (GI) effects. The participants were mostly men with localised prostate cancer, women with cervical cancer or endometrial cancer, and men and women with bladder or colorectal cancers who were undergoing primary or adjuvant radiotherapy (RT). Evidence on quality of life (QoL) was very sparse overall, and often not presented in a form that could be meta-analysed, making interpretation difficult. The main findings of the review are as follows:

Delivery techniques:

Conformal RT: Evidence on delivery techniques shows that, whilst conformal RT (3DCRT and IMRT) leads to less acute toxicity and probably less late GI toxicity than conventional RT (Summary of findings for the main comparison), evidence on beneficial effects of IMRT compared with 3DCRT on GI toxicity is of a low certainty (Summary of findings 2).

Brachytherapy (BT): In early endometrial cancer, BT techniques reduce acute GI toxicity (Summary of findings 3).

Other aspects of radiotherapy delivery:

Reduced radiation dose volume: In general, the evidence on toxicity outcomes is of a low certainty and further evidence is likely to change the estimates of effect (Summary of findings 4); evidence on other outcomes is lacking.

Bladder-volume preparation: The evidence suggesting no difference in acute and late GI toxicity between a bladder-volume preparation of 1080 ml and that of 540 ml for men undergoing RT for prostate cancer is of a low certainty, and evidence on other outcomes is lacking (Summary of findings 5).

Evening radiotherapy: Low-certainty evidence suggests that radiotherapy delivered in the evening may reduce acute GI toxicity; however, there is little evidence on other review outcomes (Summary of findings 6).

Hydrogel injections/spacers: Low-certainty evidence suggests that transperineal hydrogel spacers for men undergoing RT for prostate cancer may make little or no difference to acute and late GI (rectal) toxicity (Summary of findings 7).

Endorectal balloons (ERBs): Low-certainty evidence suggests that an ERB may reduce grade 1+ GI toxicity and late rectal bleeding; however, the evidence on other outcomes is very uncertain (Summary of findings 8).

Other interventions related to radiotherapy delivery: Findings from single studies of proton versus carbon ions, a belly board device, a positioning table, and hyperbaric oxygen had little usable data for review purposes, and the evidence on these can be considered very low certainty *(*Table 2*).*

Pharmacological interventions:

*Aminosalicylates: V*arious aminosalicylates were evaluated in several small studies. Whilst low-certainty evidence suggests that sulfasalazine may reduce grade 2+ GI toxicity, this finding was very inconsistent across the two contributing studies. In general, the evidence on aminosalicylates suggests that these types of pharmacological agents may, in fact, be associated with increased acute GI toxicity and GI symptoms, such as diarrhoea and abdominal pain/cramps, and that they probably increase the need for additional medication for GI symptom control (Summary of findings 9)

Superoxide dismutase (orgotein): Overall, the evidence on this anti-inflammatory agent is very uncertain (Summary of findings 10).

Corticosteroid enemas: The evidence on whether these make any difference to grade 2+ GI toxicity in men undergoing RT for prostate cancer is uncertain (Summary of findings 11). However, low-certainty evidence suggests that beclomethasone dipropionate enemas may reduce rectal bleeding during the 12 months post-RT.

Sucralfate: Moderate-certainty evidence, mainly derived from studies of oral sucralfate, suggests that this drug probably has little or no effect on acute GI toxicity (Summary of findings 12). The evidence on rectally-administered sucralfate (enemas) is limited, mainly due to a lack of power to determine effects.

Amifostine: Evidence suggesting a reduction in acute grade 2+ GI toxicity during RT among people with various pelvic cancers is of low certainty, with evidence on most other outcomes is very uncertain (Summary of findings 13).

Sodium butyrate: Moderate-certainty evidence suggests that this agent administered as an enema to men undergoing RT for prostate cancer probably makes little or no difference to acute GI toxicity grade 2+ (Summary of findings 14).

Selenium: Overall, the evidence on selenium is very uncertain*(* Summary of findings 15).

Other pharmacological interventions: Certain other agents show potential to reduce adverse GI effects (e.g. famotidine), but the evidence is sparse and the possible role of these agents needs further investigation (Table 2). The limited evidence on bile acid sequestrants (Summary of findings 16), misoprostol suppositories (Summary of findings 17), oral magnesium oxide (Summary of findings 18), and octreotide injections (Summary of findings 19) suggests the potential for harm with these agents, without any evidence of benefit. We found no RCT evidence on statins and ACE inhibitors.

Non-pharmacological interventions:

Diet: Evidence on diet interventions to prevent or reduce GI toxicity is generally of a low or very low certainty (or absent). Low-certainty evidence suggesting that a high-fibre diet may lead to better GI symptom scores at the end of RT and at one year post-RT, and better QoL scores at one year post-RT needs corroboration. The evidence on prophylactic elemental diet is of a very low certainty, due to sparse data and design limitations of the only available study (Summary of findings 20)

Protein supplements: Low-certainty evidence suggests that protein

supplements may reduce acute diarrhoea at three months post-RT (Summary of findings 21).

Probiotics: Low-certainty evidence suggests that probiotics may reduce diarrhoea during or at the end of RT, and may reduce the use of medication for symptom control (Summary of findings 22).

Proteolytic enzymes: The evidence on proteolytic enzymes is of a very low certainty overall (Summary of findings 23).

Glutamine: The evidence shows that glutamine does not reduce RT-related diarrhoea and may have little or no impact on other review outcomes (Summary of findings 24).

Counselling: Low-certainty evidence suggests that individualised dietary counselling may reduce acute diarrhoea at the end of RT, at three months and at five years post-RT (Summary of findings 25). It may also improve some QoL measures.

Other non-pharmacological interventions: Certain other interventions, such as green tea tablets and curcumin (turmeric), had only one small study contributing sparse data.

Overall completeness and applicability of evidence

Evidence of effectiveness for most interventions evaluated is incomplete, particularly for late effects. In addition, we found very little evidence on QoL. Even where data were available, it was often incompletely reported (e.g. missing standard deviations of the mean), which made it difficult to perform meta-analyses for this outcome. The limited opportunities for meta-analysis might give an incomplete picture of the effects of certain interventions on QoL. We have tried to report these data narratively wherever possible; however, we have not graded this evidence.

In terms of specific interventions, there is notably no compelling evidence that IMRT leads to better GI or QoL outcomes than 3DCRT. Ongoing studies of IMRT compared with 3DCRT (NCT00326638; NCT01164150; NCT01641497; NCT01672892; NCT02151019) should increase the certainty of the relative effects of these two techniques.

Despite evidence being incomplete, for certain interventions we found sufficient evidence to support a conclusion that the intervention is not helpful, e.g. octreotide injections, misoprostol suppositories, magnesium oxide, sodium butyrate enemas, oral glutamine. For other interventions, including probiotics, corticosteroid enemas, sucralfate enemas, amifostine, bile acid sequestrants, famotidine, green tea and aspects of radiotherapy delivery, such as reduced dose volume interventions, evening radiotherapy, endorectal balloons and perineal hydrogel injections (spacers), more evidence is required.

With regard to spacers, a follow-up study of Mariados 2015 was published in 2017 and is discussed below . We found no evidence on statins and ACE inhibitors.

Quality of the evidence

The evidence is generally of a low or very low certainty, with most studies not evaluating interventions for key review outcomes, particularly GI symptom scores and QoL. Evidence was often undermined by unclear study methodology or study design limitations and small sample sizes, which led to a downgrading of the evidence due to the imprecision of the estimates. Outcomes were often assessed using unvalidated scales and were poorly controlled in terms of definition and judgements, particularly for self-reported outcomes. In addition, compliance with interventions was seldom reported. Adequate reporting of compliance with interventions is particularly problematic with dietary intervention studies. Furthermore, administering a placebo or sham diet to control arms in dietary studies might not be possible or ethical.

We found few instances of high-certainty evidence. Evidence that we rated as high-certainty included evidence on conformal versus conventional RT, which indicates that modern conformal RT techniques reduce acute GI toxicity compared with older RT techniques; evidence on brachytherapy, which indicated that brachytherapy leads to less acute grade 2+ GI toxicity compared with EBRT in early endometrial cancer; and evidence on glutamine, which indicated that it has little or no effect on diarrhoea.

Potential biases in the review process

Our pragmatic approach, due to the huge scope of the review topic, might have led to limitations in the review findings, even though most of the points highlighted below were prespecified in the protocol:

Search methods

We did not handsearch journals and conference proceedings, which might have led to some studies being missed. This was a pragmatic decision taken at protocol stage, when we felt that electronic searches would identify most relevant studies and the additional resources and time invested in handsearches could not be justified and would not add much to the yield.

Study selection

We excluded three RCTs on the basis that they randomised fewer than 20 participants (an exclusion criterion prespecified in the protocol). One study that we excluded on this basis (Khan 2000) was a pilot study evaluating the effect of misoprostol suppositories compared with placebo in 16 men undergoing primary radiotherapy for prostate cancer. This study produced statistically significant results ($P < 0.05$) in favour of improved GI toxicity scores (proctitis) with misoprostol up to 36 weeks post-RT. We found no benefit of misoprostol suppositories on GI toxicity based on one included study (Hille 2005). However, due to the limitations

of the pilot study, it seems unlikely that our conclusions on misoprostol suppositories would have been significantly different had we included it.

Another small study of a nutritional intervention (Itoh 2015) randomised 20 participants and, as such, was included at study selection stage; however, investigators only reported data for 14 participants. We retained the study as 'included' and downgraded the certainty of the evidence based on these data. It is unlikely that including this study had an impact on the review findings, but other review authors might have chosen to exclude it based on the small sample size.

In the protocol we stated that we would exclude studies evaluating dose escalation. This decision was clear-cut for most studies excluded on this basis, but the eligibility of one study needed discussion before we excluded it. The study concerned (Tacev 2005) compared hypoxy-radiotherapy (RT delivered in hypoxic conditions) versus standard RT delivery in 307 women with cervical cancer. Unfortunately the RT doses in the study differed such that the hypoxic condition was not the only difference between intervention and control arms, with a higher dose (dose escalation) given to participants in the hypoxy-RT arm. Despite the higher RT dose, gastrointestinal toxicity was reduced with hypoxy-RT; for example, acute grade 2+ diarrhoea occurred in 8/155 versus 18/152 in the intervention and control arms, respectively. Similar reductions in late effects were also reported. Therefore, whilst we excluded this study, we felt that the potential benefit of hypoxy-RT (without dose escalation) on GI toxicity and survival needs further evaluation in RCTs.

In one included study of sucralfate versus placebo (Valls 1991), 10/34 (29%) participants had colostomies (7 and 3 participants in the sucralfate and placebo groups, respectively). Whilst we had specified in the protocol that we would exclude studies with more than 20% ineligible participants, excluding this study with a majority of eligible participants did not seem justifiable, as we considered that the direction of bias would most likely favour the placebo group and that the magnitude of bias in this instance would be relatively small. After discussion, we therefore decided to include the study and assessed it as having a high risk of bias. However, this study ended up contributing no data to the review meta-analyses.

Whilst toxicity outcomes were reported in all included studies, not all studies reported toxicity outcomes in a form that we could use in our meta-analyses. In most instances, this was due to the studies not being fully reported and available as conference abstracts only. However, Valls 1999, for example, reported toxicity in terms of mean number of stools and anti-diarrhoeal tablets required during the assessment period. In the absence of a study reporting our specific review outcomes, we attempted to capture these other GI toxicity outcomes narratively.

One study identified by the November 2017 top-up search (Ni 2017) remains in the Studies awaiting classification section of the review. This Chinese paper is awaiting translation and will be evaluated in the next update of the review, along with any other newly-reported IMRT studies, at least five of which are currently ongoing (see Ongoing studies).

Data extraction and analysis

Where studies reported toxicity data for numerous time points during RT, we used the data from the time point with the most events in the intervention arm (worst outcome), to ensure that any evidence of harm was not underestimated. (For the purposes of this review, we considered overestimation of toxicity preferable to underestimation). Missing denominators and standard deviations were a common feature of many studies, as was the reporting of results as percentages. Where possible we calculated these missing data from the available information, e.g. percentages reported, and Cochrane tools. We noted all instances in which we did this and considered the data to be at high risk of bias for the outcome concerned. We also took this into account when grading the evidence.

We used the random-effects model for all meta-analysis, irrespective of the statistical heterogeneity, as at the protocol stage we anticipated that clinical heterogeneity with respect to study population and interventions would be high across the included studies. Had we used a fixed-effect model, certain analyses would have had a more precise effect estimate that demonstrated benefit, as opposed to an effect showing no clear difference. An example of this is in Analysis 1.2 (conformal RT vs conventional RT, late grade 2+ GI toxicity), for which a fixed-effect model would have given a RR of 0.59 (0.36 to 0.97).

The doses and strains in the probiotic preparations evaluated varied quite widely across studies, but data were generally very sparse. Where more than one study contributed data to an analysis, we pooled the data because we found the evidence to be of a low to very low certainty, whether we pooled the data or not. Future versions of this review or other probiotic reviews that include the pending data from ongoing trials might find meaningful differences between probiotic preparations according to the strain and number of colony-forming units if the studies are subgrouped accordingly.

We had planned to extract continuous data for QoL meta-analysis, but subsequently found that it was occasionally reported as a categorical variable (e.g. Mariados 2015 reported the proportion of participants experiencing a minimally-important difference in QoL). Where this was the case, we described these data narratively.

Limitations of our outcome measures

Whilst we extracted data on acute and late toxicity according to severity grades where they were reported separately, we did not analyse these data according to the different grades, but rather grouped grades 2, 3, and 4 together in the outcome 'acute grade 2+ GI toxicity'. As a secondary outcome, we also grouped grades 1 or higher in the outcome 'acute grade 1+ GI toxicity'. We had prespecified this approach in the protocol. However, it might be considered a rather blunt approach for those wishing to know relative

differences in severe (grade 3 or 4) GI toxicity, for example. Our impression, following data extraction and evidence synthesis, was that although certain studies in which the overall number of grade 1+ (or grade 2+) GI toxicity events were similar between groups but in which fewer severe (grade 3 or 4) events were experienced in one of the groups, these data were generally sparse and unlikely to have substantially impacted the review findings on GI toxicity; i.e. evidence on grade 3 or grade 4 toxicity would probably have been graded very low-certainty evidence due to imprecision.

With regard to the evidence on the outcomes for individual GI symptoms (grade 2+), e.g. rectal bleeding, we found that many studies reported 'any grade' of these symptoms and we included these in our analyses where grade 2+ data were lacking, noting in the footnotes to the forest plots the fact that these data were ungraded. Depending on whether one considers 'any grade' to be more clinically meaningful than grade 2+, one might consider these estimates of effect to be under- or overestimated. However, the grading of the overall evidence, which would have been downgraded for design limitations (risk of bias), should have adequately captured the uncertainty introduced due to these outcome reporting differences.

Given the vast scope of the review, we focused on person-centred outcomes. However, these findings were limited by a lack of consistency between studies in the use of validated scales and tools. Certain other outcomes not included in the review might have provided useful additional information on some interventions. For example, certain objective measures of GI toxicity, such as faecal calprotectin, endoscopic findings and gastrointestinal histology, have also been studied. We discuss below, in Agreements and disagreements with other studies or reviews those included studies evaluating endoscopic findings. It is also important to note that some of the included interventions might have important effects on non-GI-related outcomes that we have not evaluated, e.g. effects on urinary or sexual outcomes.

Interpretation of the evidence

We reported the evidence in a systematic way using EPOC guidance (EPOC 2015) and presenting only the prespecified outcomes in the 'Summary of findings' tables. Thus, in a few instances, evidence suggesting potential harms or benefits does not appear in the 'Summary of Findings' table. This is in accordance with standard Cochrane methodology, but it does mean that not all important outcomes are reflected in the tables (although they are reported in the review text). We have summarised the findings of small (underpowered) single studies in Table 2.

Lastly, as mentioned in the Overall completeness and applicability of evidence, we did not grade narrative evidence on GI symptom scores and QoL outcomes, and not doing so might have underestimated the overall completeness of some of the evidence on specific interventions (e.g. counselling interventions and prerectal spacers).

Agreements and disagreements with other studies or reviews

Some individual studies have drawn conclusions about the possible benefit of interventions that are not consistent with our findings. This occurred often with small underpowered studies, such as those documented in Table 2. For example, in Muecke 2010 authors concluded that selenium "reduces the number of episodes and severity of RT-induced diarrhoea". As the number of episodes of diarrhoea was not an outcome for our review, it is possible that this effect was not captured by review analyses and therefore our conclusions about selenium differ from Muecke 2010 (we found limited evidence suggesting no difference in diarrhoea). Several included studies also covered objective outcomes which were not included in the review, particularly endoscopic findings (Fuccio 2011; Hovdenak 2005; Katsanos 2010; Kouloulias 2005; Kouvaris 2003; Maggio 2014; Prada 2009; Van Lin 2007); however, most studies did not correlate the objective findings with participant-reported outcomes (GI symptoms). Various scoring measures for endoscopic findings were used, including the Vienna Rectoscopy Score (VRS) and scales based on the World Organization for Digestive Endoscopy terminology, with severity grading from 0 to 4. Two studies graded telangiectasia according to Wachter 2000 criteria (Prada 2009; Van Lin 2007). Two studies reported histology in addition to endoscopic findings (Hovdenak 2005; Katsanos 2010). Katsanos 2010 evaluated amifostine compared with no amifostine and found little difference between groups with regard to late grade 2+ mucositis at least six months after RT (7/21 versus 6/23 for amifostine and control groups respectively), but reported more acute grade 2+ mucositis in the control group at the completion of RT (0/21 versus 4/23 for amifostine and control groups, respectively). This study reported that correlation between histology and endoscopic scores was poor, and that endoscopy underestimated mucosal injury identified by histology. Another study of amifostine (Kouvaris 2003) reported "more severe rectal mucositis" in the control group at one to two days after RT, but this was not quantified in the report. Similarly, a study of different routes of administration of amifostine (subcutaneous versus rectal routes) (Kouloulias 2005) gave no quantitative data but reported that rectosigmoidoscopy revealed greater rectal mucositis with the subcutaneous route than the rectal route at one to two days after completion of RT. Positive findings were reported by Prada 2009 (transperineal hydrogel compared with no intervention) for moderate to severe (T2 - 3) telangiectasia (2/36 versus 12/33 at 13 to 24 months; median 18 months; P = 0.002). Fuccio 2011 reported no difference at three months post-RT, but at 12 months post-RT fewer participants in the beclomethasone group had VRSs of grade 2 or more (22/55 versus 40/59, P = 0.028). The VRS was significant lower (better) in the beclomethasone group of the study. Hovdenak 2005 (oral sucralfate versus placebo) reported that there was no difference between study arms in endoscopy findings or histology during and at two weeks post-RT. Maggio 2014 (sodium butyrate enemas) also reported no difference in endoscopy find-

ings, assessed at week six of RT, between treatment and placebo arms. A study of endorectal balloons (ERBs) (Van Lin 2007) reported that high-grade telangiectasia (T2 - 3) was significantly less common in the ERB group compared with no intervention at one and two years post-RT; however, overall rates of T2 - 3 during the two-year follow-up were not significantly different (22/24 versus 21/24 for ERB and no-ERB groups, respectively). This study also reported a trend towards less rectal bleeding in the ERB group (3/24 versus 8/24; P = 0.088). These objective findings are interesting and could have added to the body of review evidence.

A Cochrane Review of diet interventions (Henson 2013) used a different approach to ours, by pooling the data of the different diet interventions. Authors concluded that any diet intervention improved patient outcomes and graded these findings as moderate-certainty, which is an interesting interpretation of existing evidence on diet. It could well be that the intensive dietary monitoring and guidance associated with any of the diet interventions evaluated has a positive effect on patient outcomes. This interpretation is partly supported by our review findings on counselling interventions, which suggested that individualised dietary counselling might have a positive impact on toxicity and QoL outcomes.

There have also been non-Cochrane reviews conducted on probiotics (Fuccio 2011; Hamad 2013). Hamad 2013 performed meta-analysis and concluded that probiotics may have a beneficial effect in the prevention of radiation-induced diarrhoea, which is in agreement with our findings on probiotics. However the evidence in Hamad 2013 was not formally graded and the text conclusions differ slightly from the abstract conclusions in the certainty of the evidence, with the text stating "may have a role" and the abstract stating that probiotics have a "probable beneficial effect" on diarrhoea prevention.

A 2015 review on preventative medical therapies to reduce radiotherapy-related toxicity (Fuccio 2015) did not perform meta-analysis or grade the evidence. Despite the limitations of our review, as discussed in Potential biases in the review process, its strength lies in the systematic approach that we have taken to a wide and diverse range of interventions. By including the same person-centred outcomes for all interventions and having the evidence graded systematically by the same team of review authors using the GRADE approach, this review should enable researchers, clinicians, funders and other stakeholders to readily compare evidence on the individual interventions. We hope that it will also help to stimulate person-centred research appropriate to different settings and contexts, and that it will prevent resource wastage by directing research towards interventions that have the potential to make a difference to people's lives.

AUTHORS' CONCLUSIONS

Implications for practice

Conformal radiotherapy techniques are an improvement on older radiotherapy techniques. IMRT may be better than 3DCRT in terms of GI toxicity but the evidence to support this is uncertain. There is insufficient high-quality evidence to support the use of any other prophylactic intervention evaluated, and evidence on several of the potential interventions shows that they have no role to play in reducing RT-related GI toxicity. In the absence of better evidence on preventive interventions to reduce GI side effects, an individualised, person-centred approach with ongoing monitoring of nutrition and GI symptomatology, during and after RT, seems prudent, to ensure timely management of symptoms as they arise. This approach is likely to require a multidisciplinary team of oncologists, dietitians, gastroenterologists and other support staff, which might require organisational changes in some settings.

Implications for research

There are 12 ongoing trials registered with clinical trials registries that are relevant to this review: these included two trials of brachytherapy (NCT00807768; NCT01839994), one trial of a diet intervention (NCT02516501), three trials of probiotics (NCT01706393; NCT01790035; NCT02351089), five trials of IMRT (NCT01164150; NCT01641497; NCT01672892; NCT02151019; NCT00326638) and one trial of acupuncture Asadpour 2017.

Long-term follow-up data are awaited on a trial of sulfasalazine compared with placebo (Miller 2016).

Evidence on the following interventions is incomplete or lacking and the evidence base could benefit from further research:

- Endorectal balloons and prerectal spacers
- Evening delivery of RT, reduced dose volume interventions, hypoxic RT
- Pharmacological agents with free radical scavenging properties, including amifostine and famotidine
- Non-pharmacological interventions, including single nutrient and other diets, probiotics and green tea
- Enemas, including sucralfate enemas and corticosteroid enemas
- Statins and ACE inhibitors

Adherence to certain interventions, particularly dietary ones, can be challenging for study participants; measuring and assessing compliance should therefore be integral to these types of studies, to provide the high-certainty evidence needed in this field.

Much research to date has been investigator-led and might have lacked the resources (including a multidisciplinary team and sufficient funding) necessary to conduct high-quality studies, partic-

ularly ensuring adequate sample size, compliance and long-term follow-up. This may partly be due to the fact that preventing and managing radiation-induced toxicity is not the responsibility of a single type of clinician. Investigators considering conducting research in this field should ensure that their studies are well-designed, with multidisciplinary collaboration, and adequately powered to answer their research question, with adherence to CONSORT guidelines (CONSORT 2012) for reporting of findings.

A similar Cochrane Review of treatment interventions for acute radiation-induced GI toxicity might be of value, as treatment of acute GI toxicity might impact the development of late GI toxicity.

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REFERENCES

References to studies included in this review

Ahmad 2010 *{published data only}*

Ahmad IU, Forman JD, Sarkar FH, Hillman GG, Health E, Vaishampayan U, et al. Soy isoflavones in conjunction with radiation therapy in patients with prostate cancer. Nutrition and Cancer 2010; Vol. 62, issue 7:996–1000.

Arafat 2016 *{published data only}*

Arafat W, Darwish A, El Hussiny G. Comparison between standard and reduced volume radiotherapy in bladder preservation trimodality protocol for muscle invasive bladder cancer patient. *Annals of Oncology* 2012;**37th ESMO Congress. 2012 September 28-October 2nd; Vienna Austria**:ix265.

* Arafat W, Darwish A, Naoum GE, Sameh W, El Husseiny G, Abd-El-Gawad F, et al. Comparison between standard and reduced volume radiotherapy in bladder preservation trimodality protocol for muscle-invasive bladder cancer patients. *Ecancermedicalscience; www.ncbi.nlm.nih.gov/pmc/articles/PMC5102689/* 2016;**10**:682; eCollection 2016.

Arregui Lopez 2012 *{published data only}*

* Arregui López E, Bueno Serrano C, Quintana Navarro G, Rodríguez Liñán M, Béjar Luque A, Rivín del Campo E, et al. Steady diet as prophylaxis of acute diarrhea in preoperative pelvic radiotherapy of rectal adenocarcinoma. *Radiotherapy and Oncology* 2012;**Annual Conference of the European Society for Radiotherapy and Oncology, ESTRO 31. 2012 May 9-13; Barcelona, Spain**:S109.

Lopez AE, Serrano BC, Navarro QG, Linan RM, Luque BA, Rivin del Campo E, et al. Steady diet as prophylaxis of acute diarrhea in preoperative pelvic radiotherapy of rectal adenocarcinoma. *Reports of Practical Oncology and Radiotherapy* 2013;**17th Meeting of the Radiation Oncology Spanish Society, SEOR 2013. 2013 June 18-21; Vigo Spain**:S111.

Athanassiou 2003 *{published data only}*

Athanassiou H, Antonadou D, Coliarakis N, Kouveli A, Synodinou M, Paraskevaidis M, et al. Protective effect of amifostine during fractionated radiotherapy in patients with pelvic carcinomas: results of a randomized trial. *International Journal of Radiation Oncology, Biology, Physics* 2003;**56**(4):1154–60.

Baughan 1993 *{published data only}*

Baughan CA, Canney PA, Buchanan RB, Pickering RM. A randomized trial to assess the efficacy of 5-aminosalicylic acid for the prevention of radiation enteritis. *Clinical Oncology (Royal College of Radiologists)* 1993;**5**(1):19–24.

Botten 2015 *{published data only}*

Botten RJ, DiMatteo AC, Sharma KG, Dinning PG, Higgs B, Fraser RJ, et al. Endorectal balloon (ERB) during image guided radiation therapy (IGRT) for carcinoma of the prostate (CAP) reduces gastrointestinal (GI) dysfunction and improves health related quality of life (HRQOL) scores at 1 year. *Gastroenterology* 2015;**148**(4 SUPPL. 1):S297.

Chang 2016 *{published data only}*

Chang L, Li L, Li W, Jiang M, Jv Y, Wang L, et al. Research on radiotherapy at different times of the day for inoperable cervical cancer. *International Journal of Clinical Pharmacology and Therapeutics* 2016;**54**(11):856–64.

Chary 1984 *{published data only}*

Chary S, Thomson DH. A clinical trial evaluating cholestyramine to prevent diarrhea in patients maintained on low-fat diets during pelvic radiation therapy. *International Journal of Radiation Oncology, Biology, Physics* 1984;**10**(10): 1885–90.

Chitapanarux 2010 *{published data only}*

Chitapanarux I, Chitapanarux T, Traisathit P, Kudumpee S, Tharavichitkul E, Lorvidhaya V. Randomized controlled trial of live lactobacillus acidophilus plus bifidobacterium

bifidum in prophylaxis of diarrhea during radiotherapy in cervical cancer patients. *Radiation Oncology (London, England)* 2010;**5**:31.

Chopra 2015 *{published data only}*

Chopra S, Engineer R, Mahantshetty U, Misra S, Phurailatpam R, Paul SN, et al. Protocol for a phase III randomised trial of image-guided intensity modulated radiotherapy (IG-IMRT) and conventional radiotherapy for late small bowel toxicity reduction after postoperative adjuvant radiation in Ca cervix. BMJ Open 2012; Vol. 2, issue 6:pii: e001896.

* Chopra S, Engineer R, Mahantshetty UM, Dora T, Kannan S, Phurailatpam R, et al. Phase III RCT of postoperative adjuvant conventional radiation (3DCRT) versus IGIMRT for reducing late bowel toxicity in cervical cancer (PARCER) (NCT01279135/CTRI2012/120349): Results of interim analyses. *International Journal of Radiation Oncology, Biology, Physics* 2015;**57th Annual Meeting of the American Society for Radiation Oncology, ASTRO 2015 October 18-21**:S4.

Dale 2001 *{published data only}*

Dale PS, Tamhankar CP, George D, Daftary GV. Co-medication with hydrolytic enzymes in radiation therapy of uterine cervix: evidence of the reduction of acute side effects. *Cancer Chemotherapy and Pharmacology* 2001;**47 Suppl**:S29–34.

Dearnaley 1999 *{published data only}*

Dearnaley DP, Khoo VS, Norman AR, Meyer L, Nahum A, Tait D, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet* 1999;**353**(9149):267–72.

Delia 2007 *{published data only}*

Delia P, Sansotta G, Donato V, Frosina P, Messina G, De Renzis C, et al. Use of probiotics for prevention of radiation-induced diarrhea. *World Journal of Gastroenterology* 2007;**13**(6):912–5.

Delia P, Sansotta G, Donato V, Frosina P, Salatino A, Messina G, et al. Use of probiotics for prevention of radiation-induced diarrhea. *Tumori* 2007;**93**(2):suppl 1-6.

* Delia P, Sansotta G, Donato V, Messina G, Frosina P, Pergolizzi S, et al. Prevention of radiation-induced diarrhea with the use of VSL#3, a new high-potency probiotic preparation. *American Journal of Gastroenterology* 2002;**97**(8):2150–2.

De Maria 1992 *{published data only}*

De Maria D, Falchi AM, Venturino P. Adjuvant radiotherapy of the pelvis with or without reduced glutathione: a randomized trial in patients operated on for endometrial cancer. *Tumori* 1992;**78**(6):374–6.

Demers 2014 *{published data only}*

Demers M, Dagnault A, Desjardins J. A randomized double-blind controlled trial: impact of probiotics on diarrhea in patients treated with pelvic radiation. *Clinical Nutrition* 2014;**33**(5):761–7.

Germain I, Desjardins J, Demers M, Dagnault A. Phase III study: Impact of probiotics on diarrhea in patients treated with pelvic radiation. *International Journal of Radiation Oncology, Biology, Physics* 2011;**53rd Annual Meeting of the American Society for Radiation Oncology, ASTRO 2011 October 2-6 2; Miami Beach, FL USA**:S667–8.

Emami 2014 *{published data only}*

Emami H, Nikoobin F, Roayaei M, Ziya HR. Double-blinded, randomized, placebo-controlled study to evaluate the effectiveness of green tea in preventing acute gastrointestinal complications due to radiotherapy. *Journal of Research in Medical Sciences* 2014;**19**(5):445–50.

Esco 2004 *{published data only}*

Esco R, Valencia J, Coronel P, Carceller JA, Gimeno M, Bascon N. Efficacy of orgotein in prevention of late side effects of pelvic irradiation: a randomized study. *International Journal of Radiation Oncology, Biology, Physics* 2004;**60**(4):1211–9.

Fuccio 2011 *{published data only}*

Fuccio L, Alessandra G, Liboria L, Cennamo V, Cecconi L, Cecconi A, et al. Topical rectal beclometasone dypropionate for the prevention of radiation-induced proctopathy: a prospective, randomized, double-blind, placebo controlled, endoscopy-based study. *Radiotherapy and Oncology* 2010; **European Society for Therapeutic Radiology and Oncology, ESTRO 29, 2010 September 12-16; Barcelona Spain**:S197.

Fuccio L, Guido A, Laterza L, Eusebi LH, Busutti L, Bunkheila F, Barbieri E, et al. Preventive treatment with topical rectal beclo-methasone dipropionate reduces post-radiation risk of bleeding in patients irradiated for prostate cancer: A randomized controlled trial. *Digestive and Liver Disease* 2011;**17th National Congress of Digestive Diseases - Italian Federation of Societies of Digestive Diseases, FISMAD, 2011 March 5-9; Turin Italy**:S133–4.

* Fuccio L, Guido A, Laterza L, Eusebi LH, Busutti L, Bunkheila F, Barbieri E, et al. Randomised clinical trial: preventive treatment with topical rectal beclomethasone dipropionate reduces post-radiation risk of bleeding in patients irradiated for prostate cancer. *Alimentary Pharmacology & Therapeutics* 2011;**34**(6):628–37.

Gandhi 2013 *{published data only}*

Gandhi AK. Long term clinical outcome and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: updated results from a prospective randomized study. *Journal of Cancer Research and Therapeutics* 2014;**36th Annual Conference of the Association of Radiation Oncologists of India, AROICON 2014**:S43.

Gandhi AK, Rath GK, Sharma DN, Sharma S, Kumar S, Thulkar S, et al. Chronic gastrointestinal toxicity in locally-advanced carcinoma cervix treated with intensity modulated versus conventional pelvic radiation therapy: Results from a prospective randomized study. *International Journal of Radiation Oncology, Biology, Physics* 2103;**55th Annual Meeting of the American Society for Radiation**

Oncology, ASTRO 2013, September 22-25; Atlanta, GA USA:S32–3.

Gandhi AK, Rath GK, Sharma DN, Subramani V, Sharma S, Manigandan D, et al. Acute gastrointestinal and genitourinary toxicities in locally advanced carcinoma cervix treated with intensity modulated versus conventional pelvic radiation therapy: Results from a prospective randomized study. International Journal of Radiation Oncology, Biology, Physics. 2012; Vol. 54th Annual Meeting of the American Society for Radiation Oncology, ASTRO 2012, October 28–31; Boston, MA USA:S436.

Gandhi AK, Rath GK, Sharma DN, Subramani V, Sharma S, Manigandan D, et al. Early clinical outcomes of intensity modulated versus conventional pelvic radiation therapy for locally advanced carcinoma cervix: a prospective randomized study. International Journal of Radiation Oncology, Biology, Physics. 2012; Vol. 54th Annual Meeting of the American Society for Radiation Oncology, ASTRO 2012, October 28–31; Boston, MA USA:S17–8.

* Gandhi AK, Sharma DN, Rath GK, Julka PK, Subramani V, Sharma S, et al. Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study. *International Journal of Radiation Oncology, Biology, Physics* 2013;**87**(3):542–8.

Gandhi AK, Sharma DN, Rath GK, Julka PK, Subramani V, Sharma S, et al. Long-term clinical outcome and late toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: updated results from a prospective randomized study. *International Journal of Radiation Oncology, Biology, Physics* 2015;**57th Annual Meeting of the American Society for Radiation Oncology, ASTRO 2015 October 18-21; San Antonio, Texas, USA**:E257–8.

Rath G, Gandhi AK, Sharma DN, Kumar S, Julka PK. Clinico-dosimetric correlation for acute and chronic gastrointestinal toxicity in patients of locally advanced carcinoma cervix treated with conventional versus IMRT: an analysis from a prospective randomized trial. *International Journal of Radiation Oncology, Biology, Physics* 2014; **56th Annual Meeting of the American Society for Radiation Oncology, ASTRO 2014 September 14-17; San Francisco, CA USA**:S184–5.

Garcia-Peris 2016 ***{published data only}***

Garcia-Peris P, Velasco C, Hernandez M, Lozano MA, Paron L, De La Cuerda C, et al. Effect of inulin and fructo-oligosaccharide on the prevention of acute radiation enteritis in patients with gynecological cancer and impact on quality-of-life: A randomized, double-blind, placebo-controlled trial. *European Journal of Clinical Nutrition* 2016;**70**(2):170–4.

Garcia-Peris P, Velasco C, Lozano MA, Moreno Y, Paron L, de la Cuerda C, et al. Effect of a mixture of inulin and fructo-oligosaccharide on Lactobacillus and Bifidobacterium intestinal microbiota of patients receiving radiotherapy: a randomised, double-blind, placebo-controlled trial. *Nutricion Hospitalaria* 2012;**27**(6):1908–15.

Gaya 2013 ***{published data only}***

Gaya A, Brulinski P, Morris SL, Ball KA, Greener AG, Corcoran S, et al. Evaluation of a Belly Board immobilisation device for rectal cancer patients receiving pre-operative chemoradiation. *Journal of Radiotherapy in Practice* 2013;**13**(4):403–9.

Giralt 2008 ***{published data only}***

Giralt J, Regadera JP, Verges R, Romero J, De la Fuente I, Biete A, et al. Effects of probiotic Lactobacillus casei DN-114 001 in prevention of radiation-induced diarrhea: results from multicenter, randomized, placebo-controlled nutritional trial. *International Journal of Radiation Oncology, Biology, Physics* 2008;**71**(4):1213–9.

Gudipudi 2014 ***{published data only}***

Gudipudi GK, Del Priore G, Alluri KR. Comparing intensity-modulated radiotherapy and conventional external beam radiotherapy in cervical cancer. *Gynecologic Oncology* 2014;**45th Annual Meeting on Women's Cancer of the Society of Gynecologic Oncology, SGO 2014 March 22-25; Tampa, FL USA**:13.

Gupta 2009 ***{published data only}***

Gupta D, Shukla P, Bisht SS, Aggarwal A, Dhawan A, Pant MC, et al. Comparative study of efficacy, tolerability of four field box technique vs two field anterior posterior technique in locally advanced carcinoma cervix a prospective analysis: a prospective analysis. *Cancer Biology & Therapy* 2009;**8**(9): 759–64.

Habl 2016 ***{published data only}***

Habl G, Uhl M, Katayama S, Kessel KA, Hatiboglu G, Hadaschik B, et al. Acute toxicity and quality of life in patients with prostate cancer treated with protons or carbon Ions in a prospective randomized phase II study - the IPI trial. *International Journal of Radiation Oncology, Biology, Physics* 2016;**95**(1):435–43.

Hejazi 2013 ***{published data only}***

Hejazi J, Rastmanesh R, Taleban FA, Molana SH, Ehtejab G. A pilot clinical trial of radioprotective effects of curcumin supplementation in patients with prostate cancer. *Journal of Cancer Science & Therapy* 2013;**5**(10):320–4.

Henriksson 1990 ***{published data only}***

Henriksson R, Arevarn M, Franzen L, Persson H, Stendahl U. Beneficial effects of sucralphate in radiation induced diarrhea. *European Journal of Gynaecological Oncology* 1990; **11**(4):299–302.

Henriksson 1991 ***{published data only}***

Henriksson R, Franzen L, Littbrand B. Effects of sucralfate on acute and late bowel discomfort following radiotherapy of pelvic cancer. *Journal of Clinical Oncology* 1992;**10**(6): 969–75.

Henriksson R, Franzen L, Littbrand B. Prevention and therapy of radiation-induced bowel discomfort. *Scandinavian Journal of Gastroenterology* 1992;**191** (Supplement):7–11.

Henriksson R, Franzen L, Littbrand B. Prevention of irradiation-induced bowel discomfort by sucralfate: a double-blind, placebo-controlled study when treating

localized pelvic cancer. *American Journal of Medicine* 1991; **91**(2A):151S–7S.

Hille 2005 *{published data only}*

* Hille A, Schmidberger H, Hermann RM, Christiansen H, Saile B, Pradier O, et al. A phase III randomized, placebo-controlled, double-blind study of misoprostol rectal suppositories to prevent acute radiation proctitis in patients with prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2005;**63**(5):1488–93.
Kertesz T, Herrmann MK, Zapf A, Christiansen H, Hermann RM, Pradier O, et al. Effect of a prostaglandin--given rectally for prevention of radiation-induced acute proctitis--on late rectal toxicity. Results of a phase III randomized, placebo-controlled, double-blind study. *Strahlentherapie und Onkologie* 2009;**185**(9):596–602.

Hombrink 2000 *{published data only}*

Hombrink J, Frohlich D, Glatzel M, Krauss A, Thiel HJ, Meier J, et al. Prevention of radiation-induced diarrhea by smectite. Results of a double-blind randomized, placebo-controlled multicenter study. *Strahlentherapie und Onkologie* 2000;**176**(4):173–9.

Hovdenak 2005 *{published data only}*

Hovdenak N, Sorbye H, Dahl O. Sucralfate does not ameliorate acute radiation proctitis: randomised study and meta-analysis. *Clinical Oncology (Royal College of Radiologists)* 2005;**17**(6):485–91.

Huddart 2013 *{published data only}*

Huddart RA, Hall E, Hussain SA, Jenkins P, Rawlings C, Tremlett J, et al. Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: results of the BC2001 Trial (CRUK/01/004). *International Journal of Radiation Oncology, Biology, Physics* 2013;**87**(2):261–9.

Itoh 2015 *{published data only}*

Itoh Y, Mizuno M, Ikeda M, Nakahara R, Kubota S, Ito J, et al. A Randomized, double-blind pilot trial of hydrolyzed rice bran versus placebo for radioprotective effect on acute gastroenteritis secondary to chemoradiotherapy in patients with cervical cancer. *Evidence-Based Complementary and Alternative Medicine* 2015;**2015**:974390.

Jahraus 2005 *{published data only}*

Jahraus CD, Bettenhausen D, Malik U, Sellitti M, St Clair WH. Prevention of acute radiation-induced proctosigmoiditis by balsalazide: a randomized, double-blind, placebo controlled trial in prostate cancer patients. *International Journal of Radiation Oncology, Biology, Physics* 2005;**63**(5):1483–7.

Kardamakis 1995 *{published data only}*

Kardamakis D, Trask CW, De Bruijn KM. A double-blind comparison study of tropisetron and placebo in the prevention of radiation-induced diarrhoea [3]. *European Journal of Cancer Part a: General Topics* 1995;**31**(5):850.

Katsanos 2010 *{published data only}*

Katsanos KH, Briasoulis E, Tsekeris P, Batistatou A, Bai M, Tolis C, et al. Randomized phase II exploratory study of prophylactic amifostine in cancer patients who receive radical radiotherapy to the pelvis. *Journal of Experimental & Clinical Cancer Research* 2010;**29**:68.

Kilic 2000 *{published data only}*

* Kilic D, Egehan I, Ozenirler S, Dursun A. Double-blinded, randomized, placebo-controlled study to evaluate the effectiveness of sulphasalazine in preventing acute gastrointestinal complications due to radiotherapy. *Radiotherapy and Oncology* 2000;**57**(2):125–9.
Kilic D, Ozenirler S, Egehan I, Dursun A. Sulfasalazine decreases acute gastrointestinal complications due to pelvic radiotherapy. *Annals of Pharmacotherapy* 2001;**35**(7-8): 806–10.

Kim 2002 *{published data only}*

Kim Y, Roscoe JA, Morrow GR. The effects of information and negative affect on severity of side effects from radiation therapy for prostate cancer. *Supportive Care in Cancer* 2002; **10**(5):416–21.

Kneebone 2001 *{published data only}*

Kneebone A, Mameghan H, Bolin T, Berry M, Turner S, Kearsley J, et al. Effect of oral sucralfate on late rectal injury associated with radiotherapy for prostate cancer: a double-blind, randomized trial. *International Journal of Radiation Oncology, Biology, Physics* 2004;**60**(4):1088–97.
* Kneebone A, Mameghan H, Bolin T, Berry M, Turner S, Kearsley J, et al. The effect of oral sucralfate on the acute proctitis associated with prostate radiotherapy: a double-blind, randomized trial. *International Journal of Radiation Oncology, Biology, Physics* 2001;**51**(3):628–35.

Koper 1999 *{published data only}*

Koper PC, Jansen P, Van Putten W, Van Os M, Wijnmaalen AJ, Lebesque JV, et al. Gastro-intestinal and genito-urinary morbidity after 3D conformal radiotherapy of prostate cancer: observations of a randomized trial. *Radiotherapy and Oncology* 2004;**73**(1):1–9.
* Koper PC, Stroom JC, Van Putten WL, Korevaar GA, Heijmen BJ, Wijnmaalen A, et al. Acute morbidity reduction using 3DCRT for prostate carcinoma: a randomized study. *International Journal of Radiation Oncology, Biology, Physics* 1999;**43**(4):727–34.

Koukourakis 2000 *{published data only}*

Koukourakis MI, Kyrias G, Kakolyris S, Kouroussis C, Frangiadaki C, Giatromanolaki A, et al. Subcutaneous administration of amifostine during fractionated radiotherapy: a randomized phase II study. *Journal of Clinical Oncology* 2000;**18**(11):2226–33.

Kouloulias 2005 *{published data only}*

Kouloulias VE, Kouvaris JR, Pissakas G, Kokakis JD, Antypas C, Mallas E, et al. A phase II randomized study of topical intrarectal administration of amifostine for the prevention of acute radiation-induced rectal toxicity. *Strahlentherapie und Onkologie* 2004;**180**(9):557–62.
* Kouloulias VE, Kouvaris JR, Pissakas G, Mallas E, Antypas C, Kokakis JD, et al. Phase II multicenter randomized study of amifostine for prevention of acute radiation rectal toxicity: topical intrarectal versus subcutaneous application.

International Journal of Radiation Oncology, Biology, Physics 2005;**62**(2):486–93.

Kouvaris 2003 ***{published data only}***
Kouvaris J, Kouloulias V, Malas E, Antypas C, Kokakis J, Michopoulos S, et al. Amifostine as radioprotective agent for the rectal mucosa during irradiation of pelvic tumors. A phase II randomized study using various toxicity scales and rectosigmoidoscopy. *Strahlentherapie und Onkologie* 2003; **179**(3):167–74.

Kozelsky 2003 ***{published data only}***
Kozelsky TF, Meyers GE, Sloan JA, Shanahan TG, Dick SJ, Moore RL, et al. Phase III double-blind study of glutamine versus placebo for the prevention of acute diarrhea in patients receiving pelvic radiation therapy. *Journal of Clinical Oncology* 2003;**21**(9):1669–74.

Lips 2011 ***{published data only}***
Lips I, Van Gils C, Kotte A, Van Leerdam M, Van Der Helde U, Van Vulpen M. A double-blind placebo-controlled randomized clinical trial with magnesium oxide to reduce prostate motion for prostate cancer radiotherapy. *Radiotherapy and Oncology* 2011;**ESTRO Anniversary Conference**:S201.
* Lips IM, Van Gils CH, Kotte ANTJ, Van Leerdam ME, Franken SPG, Van Der Heide UA, et al. A double-blind placebo-controlled randomized clinical trial with magnesium oxide to reduce intrafraction prostate motion for prostate cancer radiotherapy. *International Journal of Radiation Oncology, Biology and Physics* 2011;**82**(2):653–60.

Ljubenkovic 2002 ***{published data only}***
Ljubenkovic S. HDR brachytherapy and supervoltage external beam therapy of cervical cancer: Protection of the intestinal tract during the treatment. *Archive of Oncology* 2002;**10**(1):13–7.

Maggio 2014 ***{published data only}***
Maggio A, Magli A, Rancati T, Fiorino C, Valvo F, Fellin G, et al. Daily sodium butyrate enema for the prevention of radiation proctitis in prostate cancer patients undergoing radical radiation therapy: results of a multicenter randomized placebo-controlled dose-finding phase 2 study. *International Journal of Radiation Oncology, Biology, Physics* 2014;**89**(3):518–24.

Manikandan 2015 ***{published data only}***
Annamalai M, Kunhiparambath H, Ma L, Dayanand S, Subhash G, Julka PK, et al. Randomized control trial between HDR brachytherapy and intensity modulated radiotherapy in localized prostate cancer: analysis of acute and late toxicity and health related quality of life. 2016 World Congress of Brachytherapy. 2016 June 27-29; San Francisco, CA USA. 2016:S176.
* Manikandan A, Laviraj MA, Haresh KP, Sharma DN, Gupta S, Mallick S, et al. Combined HDR brachytherapy and external beam radiotherapy vs external beam radiotherapy alone by IMRT in localized prostate cancer; interim analysis of acute genitourinary and gastrointestinal toxicity and biological dose volume parameters from a prospectiverandomized control trial. *Brachytherapy* 2015; **36th Annual Meeting of the American Brachytherapy Society, ABS 2015**:S53.

Manir 2014 ***{published data only}***
Manir K, Kallol B, Gaurav K, Arnab A, Amitabha M, Shaymal S. Role of glutamine versus placebo in prevention of acute gastrointestinal toxicity in pelvic radiotherapy: A randomized control study. *Clinical Cancer Investigation Journal* 2014;**3**(6):508–13.

Mansouri-Tehrani 2016 ***{published data only}***
Mansouri-Tehrani HS, Khorasgani MR, Roayaei M. Effects of probiotics with or without honey on radiation-induced diarrhea. *International Journal of Radiation Research* 2016; **14**:205–13.

Mariados 2015 ***{published data only}***
Hamstra DA, Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, et al. Continued benefit to rectal separation for prostate radiation therapy: final results of a phase III trial. *Journal of Radiation Oncology, Biology, Physics* 2017;**97**(5): 976–85.
* Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, Beyer D, et al. Hydrogel spacer prospective multicenter randomized controlled pivotal trial: dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy. *International Journal of Radiation Oncology, Biology, Physics* 2015;**92**(5):971–7.

Martenson 1996 ***{published data only}***
Martenson J, Hyland G, Moertel CG, Mailliard JA, O'Fallon JR, Collins RT, et al. Olsalazine is contraindicated during pelvic radiation therapy: results of a double-blind, randomized clinical trial. *International Journal of Radiation Oncology, Biology, Physics* 1996;**35**(2):299–303.

Martenson 2000 ***{published data only}***
Martenson JA, Bollinger JW, Sloan JA, Novotny PJ, Urias RE, Michalak JC, et al. Sucralfate in the prevention of treatment-induced diarrhea in patients receiving pelvic radiation therapy: A North Central Cancer Treatment Group phase III double-blind placebo-controlled trial. *Journal of clinical oncology* 2000;**18**(6):1239–45.

Martenson 2008 ***{published data only}***
Martenson JA, Halyard MY, Sloan JA, Proulx GM, Miller RC, Deming RL, et al. Phase III, double-blind study of depot octreotide versus placebo in the prevention of acute diarrhea in patients receiving pelvic radiation therapy: results of North Central Cancer Treatment Group N00CA. *Journal of clinical oncology* 2008;**26**(32):5248–53.

Martin 2002 ***{published data only}***
Martin T, Uhder K, Kurek R, Roeddiger S, Schneider L, Vogt HG, et al. Does prophylactic treatment with proteolytic enzymes reduce acute toxicity of adjuvant pelvic irradiation? Results of a double-blind randomized trial. *Radiotherapy and Oncology* 2002;**65**(1):17–22.

McGough 2008 ***{published data only}***
McGough C, Wedlake L, Baldwin C, Hackett C, Norman AR, Blake P, et al. Clinical trial: normal diet vs. partial

replacement with oral E028 formula for the prevention of gastrointestinal toxicity in cancer patients undergoing pelvic radiotherapy. *Alimentary Pharmacology & Therapeutics* 2008;**27**(11):1132–9.

McGuffin 2016 *{published data only}*

McGuffin M, Devji N, Dugas L, Carty A, Russell S, Prospero L, et al. To prep or not to prep: That is the question. *Journal of medical imaging and radiation sciences Conference:* 12th Annual Radiation Therapy Conference, rti3 2016 March 4–5; Toronto, ON Canada;**47**(1 SUPPL): S9.

Menander-Huber 1978 *{published data only}*

Edsmyr F, Huber W, Menander KB. Orgotein efficacy in ameliorating side effects due to radiation therapy. Double-blind, placebo-controlled trial in patients with bladder tumors. *Current Therapeutic Research, Clinical and Experimental* 1976;**19**(2):198–211.

Edsmyr F, Menander-Huber KB. Orgotein efficacy in ameliorating side effects due to radiation therapy. *European Journal of Rheumatology and Inflammation* 1981;**4**(2): 228–36.

* Menander-Huber KB, Edsmyr F, Huber W. Orgotein (superoxide dismutase): a drug for the amelioration of radiation-induced side effects. A double-blind, placebo-controlled study in patients with bladder tumours. *Urological Research* 1978;**6**(4):255–7.

Miller 2016 *{published data only}*

Iott MJ. Primary and secondary endpoint analysis of N08C9 (Alliance): A phase III randomized study of sulfasalazine versus placebo in the prevention of acute radiation enteritis. *Journal of Clinical Oncology* 2015 Gastrointestinal Cancers Symposium. January 15; San Francisco, CA USA;**33**(3 SUPPL 1):no pagination.

* Miller RC, Petereit DG, Sloan JA, Liu H, Martenson JA, Bearden JD, et al. N08C9 (Alliance)-a phase 3 randomized study of sulfasalazine versus placebo in the prevention of acute diarrhea in patients receiving pelvic radiation therapy. *International Journal of Radiation Oncology, biology, physics* 2013;**87**(5):1186–7.

Miller RC, Petereit DG, Sloan JA, Liu H, Martenson JA, Bearden JD, et al. N08C9 (alliance): A phase 3 randomized study of sulfasalazine versus placebo in the prevention of acute diarrhea in patients receiving pelvic radiation therapy. *International journal of Radiation Oncology, Biology, Physics* 2016: 55th Annual Meeting of the American Society for Radiation Oncology, 2013 September 22; Atlanta, GA, USA;**95**(4):1168–74.

Miller RC, Petereit DG, Sloan JA, Liu H, Martenson JA, Bearden JD, et al. Primary and secondary endpoint analysis of n08c9 (alliance): A phase 3 randomized trial of sulfasalazine versus placebo in the prevention of acute radiation enteritis. *International Journal of Radiation Oncology, Biology, Physics* 2014;**56th Annual Meeting of the American Society for Radiation Oncology, ASTRO 2014. September 14-17; San Francisco, CA USA**:S86.

Muecke 2010 *{published data only}*

Muecke R, Glatzel M, Riesenbeck D, Bernd-Skorka R, Seifert G, Buntzel J, et al. Sodium selenite in gynecologic radiation oncology - first results of a phase III study. *Trace Elements and Electrolytes* 2004;**21**(2):78–82.

Muecke R, Micke O, Schomburg L, Buentzel J, Glatzel M, Baaske D, et al. Impact of the planning volume (PTV) size on radiation-induced diarrhea following selenium supplementation - A subgroup analysis of the multicenter phase-III trial. Anticancer Research. 15th International Hamburg Symposium on Tumor Markers. 2011 May 29–31; Hamburg, Germany; Vol. 1996:S76.

Muecke R, Micke O, Schomburg L, Buentzel J, Glatzel M, Baaske D, et al. Impact of treatment planning target volumen (PTV) size on radiation induced diarrhoea following selenium supplementation in gynecologic radiation oncology - a subgroup analysis of a multicenter, phase III trial. *Radiation Oncology* 2013;**8**:72.

Muecke R, Micke O, Schomburg L, Glatzel M, Reichl B, Kisters K, et al. Multicenter, phase III trial comparing selenium supplementation with observation in gynecologic radiation oncology: follow-up analysis of the survival data 6 years after cessation of randomization. *Integrative Cancer Therapies* 2014;**13**(6):463–7.

* Muecke R, Schomburg L, Glatzel M, Berndt-Skorka R, Baaske D, Reichl B, et al. Multicenter, phase 3 trial comparing selenium supplementation with observation in gynecologic radiation oncology. *International Journal of Radiation Oncology, Biology, Physics* 2010;**78**(3):828–35.

Mullaney 2014 *{published data only}*

Mullaney L, Thirion P, Coffey M. The impact of rectal and bladder preparation in prostate radiotherapy. *Radiotherapy and Oncology* 2011;**ESTRO Anniversary Conference**.

* Mullaney LM, O'Shea E, Dunne MT, Finn MA, Thirion PG, Cleary LA, et al. A randomized trial comparing bladder volume consistency during fractionated prostate radiation therapy. *Practical Radiation Oncology* 2014;**4**(5):e203–12.

Murphy 2000 *{published data only}*

Murphy J, Stacey D, Crook J, Thompson B, Panetta D. Testing control of radiation-induced diarrhea with a psyllium bulking agent: a pilot study. *Canadian Oncology Nursing Journal* 2000;**10**(3):96–100.

Naik 2016 *{published data only}*

Naik A, Gurjar OP, Gupta KL, Singh K, Nag P, Bhandari V. Comparison of dosimetric parameters and acute toxicity of intensity-modulated and three-dimensional radiotherapy in patients with cervix carcinoma: A randomized prospective study. *Cancer Radiotherapie* 2016;**20**:370–6.

Nascimento 2014 *{published data only}*

Nascimento M, Aguilar-Nascimento JE, Caporossi C, Castro-Barcellos HM, Motta RT. Efficacy of synbiotics to reduce acute radiation proctitis symptoms and improve quality of life: a randomized, double-blind, placebo-controlled pilot trial. *International Journal of Radiation Oncology, Biology, Physics* 2014;**90**(2):289–95.

Nout 2009 *{published data only}*

De Boer SM, Nout RA, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, Van der Steen-Banasik EM, et al. Long-term impact of endometrial cancer diagnosis and treatment on health-related quality of life and cancer survivorship: results from the randomized PORTEC-2 trial. *International Journal of Radiation Oncology, Biology, Physics* 2015;**93**(4): 797–809.

Nout RA, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens L, Van Der Steen-Banasik EM, et al. Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data. *European Journal of Cancer* 2012;**48**(11): 1638–48.

* Nout RA, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, Van der Steen-Banasik EM, et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. *Journal of Clinical Oncology* 2009;**27**(21): 3547–56.

Nout RA, Smit VT, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet* 2010;**375**(9717):816–23.

O'Brien 1997 *{published data only}*

* O'Brien PC, Franklin CI, Dear KB, Hamilton CC, Poulsen M, Joseph DJ, et al. A phase III double-blind randomised study of rectal sucralfate suspension in the prevention of acute radiation proctitis. *Radiotherapy and Oncology* 1997;**45**(2):117–23.

O'Brien PC, Franklin CI, Poulsen MG, Joseph DJ, Spry NS, Denham JW. Acute symptoms, not rectally administered sucralfate, predict for late radiation proctitis: longer term follow-up of a phase III trial--Trans-Tasman Radiation Oncology Group. *International Journal of Radiation Oncology, Biology, Physics* 2002;**54**(2):442–9.

Pal 2013 *{published data only}*

Basu J, Bhattacharya B, Pal S. A prospective randomized controlled trial to study the role of sulfasalazine in prevention of acute gastro-intestinal toxicity associated with concurrent chemoradiation in carcinoma cervix. Journal of Cancer Research and Therapeutics. 2012; Vol. 34th Annual Conference of the Association of Radiation Oncologists of India, AROICON 2012 November 29 – December 2; Kolkata India:S153.

* Pal S, Adhikary SS, Bhattacharya B, Basu J, Ghosh T, Patra NB. A prospective randomized controlled trial to study the role of sulfasalazine in prevention of acute gastrointestinal toxicity associated with concurrent chemoradiation in carcinoma cervix. *Clinical Cancer Investigation Journal* 2013;**2**(2):118–21.

Pettersson 2012 *{published data only}*

* Pettersson A, Johansson B, Persson C, Berglund A, Turesson I. Effects of a dietary intervention on acute gastrointestinal side effects and other aspects of health-related quality of life: a randomized controlled trial in prostate cancer patients undergoing radiotherapy. *Radiotherapy and Oncology* 2012;**103**(3):333–40.

Pettersson A, Nygren P, Persson C, Berglund A, Turesson I, Johansson B. Effects of a dietary intervention on gastrointestinal symptoms after prostate cancer radiotherapy: long-term results from a randomized controlled trial. *Radiotherapy and Oncology* 2014;**113**(2):240–7.

Prada 2009 *{published data only}*

Prada PJ, Gonzalez H, Menendez C, Llaneza A, Fernandez J, Santamarta E, et al. Transperineal injection of hyaluronic acid in the anterior perirectal fat to decrease rectal toxicity from radiation delivered with low-dose-rate brachytherapy for prostate cancer patients. *Brachytherapy* 2009;**8**(2): 210–7.

Ravasco 2005 *{published data only}*

Ravasco P, Monteiro-Grillo I, Camilo M. Individualized nutrition intervention is of major benefit to colorectal cancer patients: Long-term follow-up of a randomized controlled trial of nutritional therapy. *American Journal of Clinical Nutrition* 2012;**96**(6):1346–53.

* Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy. *Journal of Clinical Oncology* 2005;**23**(7):1431–8.

Razzaghdoust 2014 *{published data only}*

Razzaghdoust A, Mozdarani H, Mofid B. Famotidine as a radioprotector for rectal mucosa in prostate cancer patients treated with radiotherapy. Phase I/II randomized placebo-controlled trial. *Strahlentherapie und Onkologie* 2014;**190** (8):739–44.

Resbeut 1997 *{published data only}*

Resbeut M, Marteau P, Cowen D, Richaud P, Bourdin S, Dubois JB, et al. A randomized double blind placebo controlled multicenter study of mesalazine for the prevention of acute radiation enteritis. *Radiotherapy and Oncology* 1997;**44**(1):59–63.

Rotovnik Kozjek 2011 *{published data only}*

Rotovnik Kozjek N, Kompan L, Soeters P, Oblak I, Mlakar Mastnak D, Mozina B, et al. Oral glutamine supplementation during preoperative radiochemotherapy in patients with rectal cancer: a randomised double blinded, placebo controlled pilot study. *Clinical Nutrition* 2011;**30** (5):567–70.

Salminen 1988 *{published data only}*

Salminen E, Elomaa I, Minkkinen J, Vapaatalo H, Salminen S. Preservation of intestinal integrity during radiotherapy using live Lactobacillus acidophilus cultures. *Clinical Radiology* 1988;**39**(4):435–7.

Sanguineti 2003 *{published data only}*

Sanguineti G, Franzone P, Marcenaro M, Foppiano F, Vitale V. Sucralfate versus mesalazine versus hydrocortisone in the prevention of acute radiation proctitis during conformal

radiotherapy for prostate carcinoma. A randomized study. *Strahlentherapie und Onkologie* 2003;**179**(7):464–70.

Shukla 2010 ***{published data only}***
Shukla P, Gupta D, Bisht SS, Pant MC, Bhatt ML, Gupta R, et al. Circadian variation in radiation-induced intestinal mucositis in patients with cervical carcinoma. *Cancer* 2010; **116**(8):2031–5.

Sidik 2007 ***{published data only}***
Sidik S, Hardjodisastro D, Setiabudy R, Gondowiardjo S. Does hyperbaric oxygen administration decrease side effect and improve quality of life after pelvic radiation?. *Acta Medica Indonesiana* 2007;**39**(4):169–73.

Stellermans 2002 ***{published data only}***
Stellamans K, Lievens Y, Lambin P, Van den Weyngaert D, Van den Bogaert W, Scalliet P, et al. Does sucralfate reduce early side effects of pelvic radiation? A double-blind randomized trial. *Radiotherapy and Oncology* 2002;**65**(2): 105–8.

Stryker 1979 ***{published data only}***
Stryker JA, Demers LM, Mortel R. Prophylactic ibuprofen administration during pelvic irradiation. *International Journal of Radiation Oncology, Biology, Physics* 1979;**5**(11-12):2049–52.

Stryker 1983 ***{published data only}***
Stryker JA, Chung CK, Layser JD. Colestipol hydrochloride prophylaxis of diarrhea during pelvic radiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 1983;**9**(2):185–90.

Stryker 1986 ***{published data only}***
Stryker JA, Bartholomew M. Failure of lactose-restricted diets to prevent radiation-induced diarrhea in patients undergoing whole pelvis irradiation. *International journal of radiation oncology, biology, physics* 1986;**12**(5):789–92.

Tait 1997 ***{published data only}***
Tait DM, Nahum AE, Meyer LC, Law M, Dearnaley DP, Horwich A, et al. Acute toxicity in pelvic radiotherapy; a randomised trial of conformal versus conventional treatment. *Radiotherapy and)ncology* 1997;**42**(2):121–36.

Timko 2010 ***{published data only}***
Timko J. Probiotics as prevention of radiation-induced diarrhoea. *Journal of Radiotherapy in Practice* 2010;**9**(4): 201–8.

Valls 1991 ***{published data only}***
Valls A, Algara M, Domenech M, Llado A, Ferrer E, Marin S. Efficacy of sucralfate in the prophylaxis of diarrhea secondary to acute radiation-induced enteritis. Preliminary results of a double-blind randomized trial. *Medicina Clinica* 1991;**96**(12):449–52.

Valls 1999 ***{published data only}***
Valls A, Pestchen I, Prats C, Pera J, Aragon G, Vidarte M, et al. Multicentric double blind clinical trial comparing sucralfate vs placebo for the prevention of diarrhoea secondary to pelvic irradiation. *Medicina Clinica* 1999;**113** (18):681–4.

Van Lin 2007 ***{published data only}***
Van Lin EN, Kristinsson J, Philippens ME, De Jong DJ, Van der Vight LP, Kaanders JH, et al. Reduced late rectal mucosal changes after prostate three-dimensional conformal radiotherapy with endorectal balloon as observed in repeated endoscopy. *International Journal of Radiation Oncology, Biology, Physics* 2007;**67**(3):799–811.

Viani 2016 ***{published data only}***
Viani GA, Viana BS, Martin JE, Rossi BT, Zuliani G, Stefano EJ. Intensity-modulated radiotherapy reduces toxicity with similar biochemical control compared with 3-dimensional conformal radiotherapy for prostate cancer: a randomized clinical trial. *Cancer* 2016;**122**(13):2004–11.

Vidal-Casariego 2014 ***{published data only}***
Vidal Casariego A, Calleja-Fernández A, Cano-Rodríguez I, Cordido-Carballido F, Ballesteros-Pomar MD. Oral glutamine during radiotherapy does not prevent subacute radiation enteritis: A randomized controlled trial. *Clinical Nutrition* 2013;**35th European Society for Clinical Nutrition and Metabolism, ESPEN Congress**:PP085.
Vidal-Casariego A, Calleja-Fernandez A, Cano-Rodriguez I, Cordido F, Ballesteros-Pomar MD. Effects of oral glutamine during abdominal radiotherapy on chronic radiation enteritis: A randomized controlled trial. *Nutrition* 2015;**31** (1):200–4.
* Vidal-Casariego A, Calleja-Fernandez A, De Urbina-Gonzalez JJO, Cano-Rodriguez I, Cordido F, Ballesteros-Pomar MD. Efficacy of glutamine in the prevention of acute radiation enteritis: a randomized controlled trial. *Journal of Parenteral and Enteral Nutrition* 2014;**38**(2):205–13.

Wedlake 2012 ***{published data only}***
Wedlake L, McGough C, Klopper T, Thomas K, Lalji A, Dearnaley DP, et al. Clinical trial: Efficacy of a low or modified fat diet for the prevention of gastrointestinal toxicity in patients receiving radiotherapy treatment for pelvic malignancy. Radiotherapy and oncology. 2010; Vol. Conference: European Society for Therapeutic Radiology and Oncology, ESTRO 29. Barcelona Spain:S364.
* Wedlake LJ, McGough C, Shaw C, Klopper T, Thomas K, Lalji A, et al. Clinical trial: efficacy of a low or modified fat diet for the prevention of gastrointestinal toxicity in patients receiving radiotherapy treatment for pelvic malignancies. *Journal of Human Nutrition and Dietetics* 2012;**25**(3): 247–59.

Wedlake 2017 ***{published and unpublished data}***
Wedlake LJ, Shaw C, Lalji A, Mohammed K, Essapen S, Whelan K, et al. High fibre diet, low fibre diet or habitual diet for the prevention of radiation-induced toxicity in pelvic cancer: a multi-centre randomised controlled trial. *Gut* 2015;**2nd Digestive Disorders Federation Conference, DDF 2015. 2015 June 22-25; London, UK**: A370–1.
* Wedlake LJ, Shaw C, McNair H, Lalji A, Mohammed K, Klopper T, et al. Randomized controlled trial of dietary fiber for the prevention of radiation-induced gastrointestinal toxicity during pelvic radiotherapy. American Journal of

Clinical Nutrition 2017:pii: ajcn150565. doi: 10.3945/ajcn.116.150565. [Epub ahead of print].

Yu 2015 *{published data only}*
Yu C, Zhu W, Ji Y, Guo J, Pan P, Han J, et al. A comparative study of intensity-modulated radiotherapy and standard radiation field with concurrent chemotherapy for local advanced cervical cancer. *European Journal of Gynaecological Oncology* 2015;**36**(3):278–82.

Zachariah 2010 *{published data only}*
Zachariah B, Gwede CK, James J, Ajani J, Chin LJ, Donath D, et al. Octreotide acetate in prevention of chemoradiation-induced diarrhea in anorectal cancer: randomized RTOG trial. *Journal of the National Cancer Institute* 2010;**102**(8):547–56.

References to studies excluded from this review

Akhtar 2010 *{published data only}*
Akhtar PS, Hossain MM, Masud ZM, Ruksana N, Nahar S, Nahar L, et al. A comparative study of result of treatment of cancer cervix patients treated by two separate schedules of radiotherapy. *Bangladesh Journal of Obstetetrics and Gynaecology* 2010;**25**(2):50–8.

Al-Mamgani 2008 *{published data only}*
Al-Mamgani A, Van Putten WL, Heemsbergen WD, Van Leenders GJ, Slot A, Dielwart MF, et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2008;**72**(4):980–8.

Al-Mamgani 2009 *{published data only}*
Al-Mamgani A, Heemsbergen WD, Peeters ST, Lebesque JV. Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2009;**73**(3):685–91.

Barnett 2011 *{published data only}*
Barnett GC, De Meerleer G, Gulliford SL, Sydes MR, Elliott RM, Dearnaley DP. The impact of clinical factors on the development of late radiation toxicity: results from the Medical Research Council RT01 trial (ISRCTN47772397). *Clinical Oncology* 2011;**23**(9):613–24.

Barraclough 2012 *{published data only}*
Barraclough LH, Routledge JA, Farnell DJJ, Burns MP, Swindell R, Livsey JE, et al. Prospective analysis of patient-reported late toxicity following pelvic radiotherapy for gynaecological cancer. *Radiation Oncology (London, England)* 2012;**103**(3):327–32.

Basu 2016 *{published data only}*
Basu P, Jenson AB, Majhi T, Choudhury P, Mandal R, Banerjee D, et al. Phase 2 randomized controlled trial of radiation therapy plus concurrent interferon-alpha and retinoic acid versus cisplatin for stage III cervical carcinoma. *International Journal of Radiation Oncology, Biology, Physics* 2016;**94**(1):102–10.

Becker-Schiebe 2016 *{published data only}*
Becker-Schiebe M, Abaci A, Ahmad T, Hoffmann W. Reducing radiation-associated toxicity using online image guidance (IGRT) in prostate cancer patients undergoing dose-escalated radiation therapy. *Reports on Practical Oncology and Radiotherapy* 2016;**21**(3):188–94.

Belcaro 2008 *{published data only}*
Belcaro G, Cesarone MR, Genovesi D, Ledda A, Vinciguerra G, Ricci A, et al. Pycnogenol may alleviate adverse effects in oncologic treatment. *Panminerva Medica* 2008;**50**(3):227–34.

Birgisson 2006 *{published data only}*
Birgisson H, Påhlman L, Gunnarsson U, Glimelius B, Swedish Rectal Cancer Trial Group. Adverse effects of preoperative radiation therapy for rectal cancer: Long-term follow-up of the Swedish Rectal Cancer Trial. *Journal of Clinical Oncology* 2005;**23**(34):8697–705.

Bittner 2008 *{published data only}*
Bittner N, Wallner K, Merrick G, Orio P, Nurani R, True L. The time gap between Pd-103 prostate brachytherapy and supplemental beam radiation does not impact on rectal morbidity or likelihood of cure. *American Journal of Clinical Oncology* 2008;**31**(3):231–6.

Boronow 1977 *{published data only}*
Boronow RC, Hickman BT. A comparison of two radiation therapy--treatment plans for carcinoma of the cervix. II. Complications and survival rates. *American Journal of Obstetrics and Gynecology* 1977;**128**(1):99–105.

Bossi 2016 *{published data only}*
Bossi A, Blanchard P. Hypofractionation for prostate cancer: a word of caution. *Lancet* 2016;**17**(4):406–7.

Bounous 1975 *{published data only}*
Bounous G, Le Bel E, Shuster J, Gold P, Tahan WT, Bastin E. Dietary protection during radiation therapy. *Stralentherapie* 1975;**149**(5):476–83.

Brabbins 2005 *{published data only}*
Brabbins D, Martinez A, Yan D, Lockman D, Wallace M, Gustafson G, et al. A dose-escalation trial with the adaptive radiotherapy process as a delivery system in localized prostate cancer: analysis of chronic toxicity. *International Journal of Radiation Oncology, Biology, Physics* 2005;**61**(2):400–8.

Brennan 2015 *{published data only}*
Brennan V, Curran B, Mc Veigh E, Farrell S, Skourou C, Dunne M, et al. Rectal cancer: Using V-MAT with avoidance sectors and avoidance structures to reduce dose to small bowel. Conference: 3 ESTRO Forum. 2015 April 24-28; Barcelona Spain. 2015:S707–8.

Bruner 2015 *{published data only}*
Bruner DW, Hunt D, Michalski JM, Bosch WR, Galvin JM, Amin M, et al. Preliminary patient-reported outcomes analysis of 3-dimensional radiation therapy versus intensity-modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group (RTOG) 0126 prostate cancer trial. *Cancer* 2015;**121**(14):2422–30.

Capirci 2001 *{published data only}*
Capirci C, Polico C, Mandoliti G. Dislocation of small bowel volume within box pelvic treatment fields, using new

'up down table' device. *International Journal of Radiation Oncology, Biology, Physics* 2001;**51**(2):465–73.

Chen 2012 ***{published data only}***
Chen AL, Terakedis B, Williams B, Gaffney D. Clinical outcomes of 3-dimensional versus IMRT postoperative pelvic radiation for gynecologic malignancies. 54th Annual Meeting of the American Society for Radiation Oncology, ASTRO 2012 October 28-31; Boston, MA USA. 2012: S452.

Dische 1999 ***{published data only}***
Dische S, Saunders MI, Sealy R, Werner ID, Verma N, Foy C, et al. Carcinoma of the cervix and the use of hyperbaric oxygen with radiotherapy: A report of a randomised controlled trial. *Radiotherapy and Oncology* 1999;**53**(2): 93–8.

Dunst 2000 ***{published data only}***
Dunst J, Semlin S, Pigorsch S, Muller AC, Reese T. Intermittent use of amifostine during postoperative radiochemotherapy and acute toxicity in rectal cancer patients. *Stralentherapie und Okologie* 2000;**176**(9):416–21.

Frøseth 2015 ***{published data only}***
Frøseth TC, Strickert T, Solli KS, Salvesen Ø, Frykholm G, Reidunsdatter RJ. A randomized study of the effect of patient positioning on setup reproducibility and dose distribution to organs at risk in radiotherapy of rectal cancer patients. *Radiation Oncology (London, England)* 2015;**10**: 217.

Fuccio 2013 ***{published data only}***
Fuccio L, Guido A. Probiotics supplementation for the prevention of gastrointestinal radiation-induced side effects: The time is now. *American Journal of Gastroenterology* 2013; **108**(2):277.

Ghaly 2003 ***{published data only}***
Ghaly M, Wallner K, Merrick G, True L, Sutlief S, Cavanagh W, et al. The effect of supplemental beam radiation on prostate brachytherapy-related morbidity: morbidity outcomes from two prospective randomized multicenter trials. *International Journal of Radiation Oncology, Biology, Physics* 2003;**55**(5):1288–93.

Guix 2010 ***{published data only}***
Guix B, Bartrina J M, Tello J I, Sole J, Ouinzanos L, Lacorte T, et al. Treatment of intermediate-or high-risk prostate cancer by dose escalation with high-dose 3D-conformal radiotherapy (HD-3D-CRT) or low-dose 3D-conformal radiotherapy plus HDR brachytherapy (LD-3D-CRT+HDRB): Early results of a prospective comparative trial. European Society for Therapeutic Radiology and Oncology, ESTRO 29. Conference Start: 2010 September 12-16; Barcelona Spain. 2010:S418.

Hamilton-Reeves 2013 ***{published data only}***
Hamilton-Reeves JM, Banerjee S, Banerjee SK, Holzbeierlein JM, Thrasher JB, Kambhampati S, et al. Short-term soy isoflavone intervention in patients with localized prostate cancer: a randomized, double-blind, placebo-controlled trial. *PLOS One* 2013;**8**(7):e68331. [DOI: 10.1371/journal.pone.0068331

Ishii 2016 ***{published data only}***
Ishii K, Ogino R, Hosokawa Y, Fujioka C, Okada W, Nakahara R, et al. Comparison of dosimetric parameters and acute toxicity after whole-pelvic vs prostate-only volumetric-modulated arc therapy with daily image guidance for prostate cancer. *British Journal of Radiology* 2016;**89**:20150930.

Kavikondala 2016 ***{published data only}***
Kavikondala M, Reddy VAP, Bhattacharya K, Upadhyay P, Seshakiren N. Validation of bone marrow sparing IMRT and comparison with standard IMRT in cervical cancer patients. 38th Annual Conference of the Association of Radiation Oncologists of India, AROICON 2016; India. 2016; Vol. 12:S32.

Khan 2000 ***{published data only}***
Khan AM, Birk JW, Anderson JC, Georgsson M, Park TL, Smith CJ, et al. A prospective randomized placebo-controlled double-blinded pilot study of misoprostol rectal suppositories in the prevention of acute and chronic radiation proctitis symptoms in prostate cancer patients. *American Journal of Gastroenterology* 2000;**95**(8):1961–6.

Kilic 2012 ***{published data only}***
Kilic D, Pak Y, Oguz M. The effect of oral nutritional supplementation including epa in rectal cancer patients undergoing preoperative chemoradiotherapy (CRT). 34th European Society for Clinical Nutrition and Metabolism, ESPEN Congress. 2012 Serptember 8-11; Barcelona Spain. 2012:165.

Kim 2016 ***{published data only}***
Kim YJ, Park JH, Yun IH, Kim YS. A prospective comparison of acute intestinal toxicity following whole pelvic versus small field intensity-modulated radiotherapy for prostate cancer. *Oncotargets and Therapy* 2016;**9**: 1319–25.

Koizumi 2005 ***{published data only}***
Koizumi M, Nishimura T, Kagiya T. Clinical trial of adverse effect inhibition with glucosides of vitamin C and vitamin E in radiotherapy and chemotherapy. *Journal of Cancer Research and Therapeutics* 2005;**1**(4):239.

Kucuktulu 2013 ***{published data only}***
Kucuktulu E, Guner A, Kahraman I, Topbas M, Kucuktulu U. The protective effects of glutamine on radiation-induced diarrhea. *Support Care Cancer* 2013;**21**(4):1071–5.

Morton 2016 ***{published data only}***
Morton G, Chung HT, McGuffin M, D'Alimonte L, Zhang L, Ravi A, et al. Early patient-reported outcomes in a randomized phase II trial of HDR monotherapy in low and intermediate risk prostate cancer. *Brachytherapy* 2016; **15**(Suppl 1):S75.

Nguyen 1998 ***{published data only}***
Nguyen LN, Pollack A, Zagars GK. Late effects after radiotherapy for prostate cancer in a randomized dose-response study: results of a self-assessment questionnaire. *Adult Urology* 1998;**51**(6):991–7.

Nout 2011 *{published data only}*
Nout RA, Van de Poll-Franse LV, Lybeert ML, Warlam-Rodenhuis CC, Jobsen JJ, Mens JW, et al. Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. *Journal of Clinical Oncology* 2011;**29** (13):1692–700.

Olofsen-Van 2001 *{published data only}*
Olofsen-Van Acht M, Van Den Berg H, Quint S, De Boer H, Seven M, Van Somsen De Koste J, et al. Reduction of irradiated small bowel volume and accurate patient positioning by use of a bellyboard device in pelvic radiotherapy of gynecological cancer patients. *Radiotherapy and Oncology* 2001;**59**(1):87–93.

Pollack 1996 *{published data only}*
Pollack A, Zagars GK, Starkschall G, Childress CH, Kopplin S, Boyer AL, et al. Conventional vs. conformal radiotherapy for prostate cancer: preliminary results of dosimetry and acute toxicity. *International Journal of Radiation Oncology, Biology, Physics* 1996;**34**(3):555–64.

Reinshagen 2012 *{published data only}*
Reinshagen M, Hoffmann W, Classen J, Mueller R, Greinwald R, Schiebe MB. Randomised, double-blind, placebo-controlled phase ii pilot study on the efficacy and tolerability of an rectal treatment with budesonide (2MG) or placebo for the prevention of acute radiation proctitis. *Gastroenterology* 2012;**142**(5):S–182.

Restivo 2015 *{published data only}*
Restivo A, Cocco IM, Casula G, Scintu F, Cabras F, Scartozzi M, et al. Aspirin as a neoadjuvant agent during preoperative chemoradiation for rectal cancer. *British Journal of Cancer* 2015;**113**(8):1133–9.

Roscoe 2009 *{published data only}*
Roscoe JA, Bushunow P, Jean-Pierre P, Heckler CE, Purnell JQ, Peppone LJ, et al. Acupressure bands are effective in reducing radiation therapy-related nausea. *Journal of Pain and Symptom Management* 2009;**38**(3):381–9.

Sheng 2013 *{published data only}*
Sheng X, Li D. A prospective clinical study of intensity modulated radiation therapy versus conventional radiotherapy in cervical cancer patients with postoperative pelvic recurrence. 18th International Meeting of the European Society of Gynaecological Oncology, ESGO 2013 October 19-22; Liverpool, UK. 2013:107.

Sirak 2014 *{published data only}*
Sirak I, Pritz J, Wei L, Tarnawski R, Mahantshetty U, Khorprasert C, et al. International evaluation of radiotherapy technology effectiveness in cervical cancer (INTERTECC) phase ii trial of intensity modulated radiotherapy (IMRT): Interim analysis and preliminary results. ESGO 2014. 2014; Vol. 24:9 SUPPL. 4 577-8.

Sorbe 2012a *{published data only}*
Sorbe B, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B. External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma - a prospective randomized study. *International Journal of Radiation Oncology, Biology, Physics* 2012;**82**(3):1249–55.

Sorbe 2012b *{published data only}*
Sorbe BG, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B. External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma: A prospective, randomized study - Quality-of-life analysis. *International Journal of Gynecological Cancer* 2012;**22**(7):1281–8.

Stojcev 2013 *{published data only}*
Stojcev Z, Krokowicz L, Krokowicz P, Szczepkowski M, Borycka-Kiciak K, Kiciak A, et al. Early treatment and prevention of the radiation proctitis - composite enemas containing sodium butyrate. *International Journal of Colorectal Diseases* 2013;**28**(12):1731–2.

Sun 2014 *{published data only}*
Sun JX, Yang N. Role of octreotide in post chemotherapy and/or radiotherapy diarrhea: Prophylaxis or therapy?. *Asia-Pacific Journal of Clinical Oncology* 2014;**10**(2):e108–13.

Tacev 2005 *{published data only}*
Tacev T, Vacek A, Ptackova B, Strnad V. Hypoxic versus normoxic external-beam irradiation of cervical carcinoma combined with californium-252 neutron brachytherapy: Comparative treatment results of a 5-year randomized study. *Strahlentherapie und Onkologie* 2005;**181**(5):273–84.

Teshima 1990 *{published data only}*
Teshima T, Inoue T, Chatani M, Ikeda H, Nishiyama K, Inoue T, et al. Radiation therapy of the para-aortic lymph nodes in carcinoma of the uterine cervix: the concurrent use of cimetidine to reduce acute and subacute side effects from radiation. *Clinical Therapeutics* 1990;**12**(1):71–7.

Timko 2013 *{published data only}*
Timko J. Effect of probiotics on the fecal microflora after radiotherapy: a pilot study. *Indian Journal of Pathology & Microbiology* 2013;**56**(1):31–5.

Uhl 2013 *{published data only}*
Uhl M, Van Triest B, Eble MJ, Weber DC, Herfarth K, De Weese TL. Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: results of a multi-institutional phase II trial. *Radiation Oncology (London, England)* 2013;**106**(2):215–9.

Ungerleider 1984 *{published data only}*
Ungerleider JT, Andrysiak TA, Fairbanks LA, Tesler AS, Parker RG. Tetrahydrocannabinol vs. prochlorperazine. The effects of two antiemetics on patients undergoing radiotherapy. *Radiology* 1984;**150**(2):598–9.

Urbancsek 2001 *{published data only}*
Urbancsek H, Kazar T, Mezes I, Neumann K. Results of a double-blind, randomized study to evaluate the efficacy and safety of Antibiophilus in patients with radiation-induced diarrhoea. *European Journal of Gastroenterology and Hepatology* 2001;**13**(4):391–6.

Vuong 2014 *{published data only}*
Vuong T, Garant A, Gallant F. Intensity-modulated radiation therapy for patients with rectal cancer. *Colorectal Cancer* 2014;**3**(3):235–8.

Widmark 1997 *{published data only}*
Widmark A, Fransson P, Franzen L, Littbrand B, Henriksson R. Daily-diary evaluated side-effects of conformal versus conventional prostatic cancer radiotherapy technique. *Acta Oncologica* 1997;**36**(5):499–507.

Wortel 2015 *{published data only}*
Wortel RC, Incrocci L, Pos FJ, Lebesque JV, Witte MG, Van Der Heide UA, et al. Acute toxicity after image-guided intensity modulated radiation therapy compared to 3D conformal radiation therapy in prostate cancer patients. *International Journal of Radiation Oncology, Biology, Physics* 2015;**91**(4):737–44.

Wortel 2016 *{published data only}*
Wortel RC, Incrocci L, Pos FJ, Van Der Heide UA, Lebesque JV, Aluwini S, et al. Late side effects after image guided intensity modulated radiation therapy compared to 3d-conformal radiation therapy for prostate cancer: Results from 2 prospective cohorts. *International Journal of Radiation Oncology, Biology, Physics* 2016;**95**(2):680–9.

Yoshioka 2014 *{published data only}*
Yoshioka Y, Konishi K, Suzuki O, Nakai Y, Isohashi F, Seo Y, et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: a dose reduction trial. *Radiotherapy and Oncology* 2014;**110**(1):114–9.

Zapatero 2010 *{published data only}*
Zapatero Ortuno J, Samper Ots PM, Lopez Carrizosa MC, Rodriguez Perez A, Saez Garrido JD, Lopez Gonzalez M, et al. Intermediate risk localized prostate cancer treated with three-dimensional conformal RT (3DCR) versus 3DCR with low dose rate brachytherapy boost (3DCR+BT). European Society for Therapeutic Radiology and Oncology, ESTRO 29. 2010 Serptember 12-16; Barcelona, Spain. 2010:S216–.

Zilli 2015 *{published data only}*
Zilli T, Bruynzeel A, Minn H, Sanchez-Saugar E, Oliveira A, Bral S, et al. Short vs protracted urethra-sparing prostate SBRT: Feasibility and early toxicity from a randomized phase II trial. 3 ESTRO Forum. 2015 April 24-28; Barcelona, Spain. 2015:S356.

References to studies awaiting assessment

Ni 2017 *{published data only}*
Ni J, Yin ZM, Yuan SH, Liu NF, Li L, Xu XX, et al. A randomized study of intensity-modulated radiation therapy versus three dimensional conformal radiation therapy for pelvic radiation in patients of post-operative treatment with gynecologic malignant tumor. *Zhonghua fu chan ke za zhi* 2017;**52**:168–74.

References to ongoing studies

Asadpour 2017 *{published data only}*
Asadpour R, Kessel KA, Bruckner T, Sertel S, Combs SE. Randomized study exploring the combination of radiotherapy with two types of acupuncture treatment (ROSETTA): study protocol for a randomized controlled trial. *Trials* 2017;**18**(1):398.

NCT00326638 *{published data only}*
NCT00326638. Randomised phase III trial of 3D conformal radiotherapy versus helical tomotherapy IMRT in high-risk prostate cancer. clinicaltrials.gov/show/NCT00326638 (first received 17 May 2006).

NCT00807768 *{published data only}*
NCT00807768. Pelvic radiation therapy or vaginal implant radiation therapy, paclitaxel, and carboplatin in treating patients with high-risk stage I or stage II endometrial cancer. clinicaltrials.gov/show/NCT00807768 (first received 12 December 2008).

NCT01164150 *{published data only}*
* NCT01164150. Prospective randomised phase II trial evaluating adjuvant pelvic radiotherapy using either IMRT or 3-dimensional planning for endometrial cancer. ICORG 09-06. clinicaltrials.gov/show/NCT01164150 (first received 16 July 2010).
O'Sullivan L, McArdle O, Gilmore J, Walsh L, Gillham C. ICORG 09-06 an ongoing prospective randomised trial comparing 3D RT with IMRT for the treatment of endometrial cancer. *Radiotherapy and Oncology* 2012; **Annual Conference of the European Society for Radiotherapy and Oncology, ESTRO 31. 2012 May 9-13; Barcelona Spain**:S243.

NCT01641497 *{published data only}*
NCT01641497. Phase III study comparing 3D conformal radiotherapy and conformal IMRT to treat endometrial cancer (TOMOGYN). clinicaltrials.gov/show/NCT01641497 (first received 16 July 2012).

NCT01672892 *{published data only}*
NCT01672892. Standard versus intensity-modulated pelvic radiation therapy in treating patients with endometrial or cervical cancer. clinicaltrials.gov/show/NCT01672892 (first received 27 August 2012).

NCT01706393 *{published data only}*
NCT01706393. The effects of probiotics supplementation on intestinal microbiome in malignancy patients who get pelvic/abdominal radiotherapy.. clinicaltrials.gov/show/NCT01706393 (first received 31 August 2012).

NCT01790035 *{published data only}*
NCT01790035. A phase I and randomized controlled phase II trial of the probiotic LGG for prevention of side effects on patients undergoing chemoradiation for gastrointestinal cancer. clinicaltrials.gov/show/NCT01790035 (first received 12 February 2013).

NCT01839994 *{published data only}*
NCT01839994. Conformal radiotherapy (CRT) alone versus CRT combined with HDR BT or stereotactic body radiotherapy for prostate cancer. clinicaltrials.gov/show/NCT01839994 (first received 25 April 2013).

NCT02151019 *{published data only}*

NCT02151019. Pre-operative 3DCRT vs IMRT for locally advanced rectal cancer (TRI-LARC). clinicaltrials.gov/show/NCT02151019 (firs treceived 30 May 2014).

NCT02351089 *{published data only}*

NCT02351089. Probiotics in radiation-treated gynecologic cancer (ProRad). clinicaltrials.gov/show/NCT02351089 (first received 30 January 2015).

NCT02516501 *{published data only}*

NCT02516501. Impact of a ketogenic diet intervention during radiotherapy on body composition (KETOCOMP). clinicaltrials.gov/show/NCT02516501 (first received 6 August 2015).

Additional references

Aluwini 2015

Aluwini S, Pos F, Schimmel E, Van Lin E, Krol S, Van der Toorn PP, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. *Lancet Oncology* 2015;**16**(3): 274–83.

Andreyev 2007

Andreyev J. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. *Lancet Oncology* 2007;**8**(11): 1007–17.

Andreyev 2012

Andreyev HJ, Davidson SE, Gillespie C, Allum WH, Swarbrick E. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. *Gut* 2012;**61**(2):179–92.

Arcangeli 2010

Arcangeli G, Saracino B, Gomellini S, Petrongari MG, Arcangeli S, Sentinelli S, et al. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2010;**78**(1):11–8.

BNF 2016

Joint Formulary Committee. *British National Formulary (BNF) 72*. London: BMJ Publishing Group Ltd and Royal Pharmaceutical Society, 2016.

Both 2012

Both S, Deville C, Bui V, Kang-Hsin Wang K, Vapiwala N. Emerging evidence for the role of an endorectal balloon in prostate radiation therapy. *Translational Cancer Research* 2012;**1**(3):227–35.

Buchi 1991

Buchi K, Moore J, Hrushesky W, Sothern R, Rubin N. Circadian rhythm of cellular proliferation in the human rectal mucosa. *Gastroenterology* 1991;**101**(2):410–5.

Cancer Res 2016

Cancer Research UK. What radiotherapy is. www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/radiotherapy/about (accessed 26 September 2016).

CCS 2016

Canadian Cancer Society. Conformal radiation therapy. www.cancer.ca/en/cancer-information/diagnosis-and-treatment/radiation-therapy (accessed 13 July 2016).

CHHiP 2016

Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated High-dose intensitiy-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncology* 2016;**17**(8): 1047–60.

CONSORT 2012

Altman DG, Moher D, Schultz KF. Improving the reporting of randomised trials: The CONSORT statement and beyond. *Statistics in Medicine* 2012;**31**(25):2985–97.

Cox 1995

Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *International Journal of Radiation Oncology, Biology, Physics* 1995;**31**(5):1342–6.

CTCAE 2010

National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (accessed 7 July 2016).

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG editor(s). *Systematic Reviews in Health Care: Meta-Analysis in Context*. 2nd Edition. London: BMJ Publication Group, 2001.

Denham 2002

Denham J, Hauer-Jensen M. The radiotherapeutic injury - a complex 'wound'. *Radiotherapy Oncology* 2002;**63**(2): 129–45.

Dennert 2006

Dennert G, Horneber M. Selenium for alleviating the side effects of chemotherapy, radiotherapy and surgery in cancer patients. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: 10.1002/14651858.CD005037.pub2

Devereux 1988

Devereux D, Chandler J, Eisenstat T, Zinkin L. Efficacy of an absorbable mesh in keeping the small bowel out of the human pelvis after surgery. *Diseases of the Colon and Rectum* 1988;**31**(1):17–21.

Dupont 2009

Dupont C, Vernisse B. Anti-diarrheal effects of diosmectite in the treatment of acute diarrhea in children: a review. *Paediatric Drugs* 2009;**11**(2):89–99.

EPOC 2015
Effective Practice, Organisation of Care (EPOC). EPOC Resources for review authors. epoc.cochrane.org/epoc-specific-resources-review-authors (accessed 6 July 2016).

Frazzoni 2015
Frazzoni L, La Marca M, Guido A, Morganti AG, Bazzoli F, Fuccio L. Pelvic radiation disease: Updates on treatment options. *World Journal of Clinical Oncology* 2015;**6**(6): 272–80.

Fuccio 2015
Fuccio L, Frazzoni L, Guido A. Prevention of pelvic radiation disease. *World J Gastrointestinal Pharmacology Therapeutics* 2015;**6**(1):1–9.

Fuhr 2015
Fuhr L, Abreu M, Pett P, Relógio A. Circadian systems biology: When time matters. *Computational and Structural Biotechnology Journal* 2015;**13**:417–26.

Gavazzi 2006
Gavazzi C, Bhoori S, Lo Vullo S, Cozzi G, Mariani L. Role of home parenteral nutrition in chronic radiation enteritis. *American Journal of Gastroenterology* 2006;**101**(2):374–9.

GLOBOCAN 2012
International Agency for Research on Cancer. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (accessed 14 Jul 2016).

Hall 2016
Hall S, Rudrawar S, Zunk M, Bernaitis N, Arora D, McDermott M, et al. Protection against radiotherapy-induced toxicity. *Antioxidants* 2016;**5**(3):E22. [DOI: 10.3390/antiox5030022

Hamad 2013
Hamad A, Fragkos K, Forbes A. A systematic review and meta-analysis of probiotics for the management of radiation induced bowel disease. *Clinical Nutrition* 2013;**32**(3): 353–60.

Henson 2013
Henson CC, Burden S, Davidson SE, Lal S. Nutritional interventions for reducing gastrointestinal toxicity in adults undergoing radical pelvic radiotherapy. *Cochrane Database of Systematic Reviews* 2013, Issue 11. [DOI: 10.1002/14651858.CD009896.pub2

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60.

Higgins 2011
Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Hoffman 2014
Hoffman KE, Voong KR, Pugh TJ, Skinner H, Levy LB, Takiar V, et al. Risk of late toxicity in men receiving dose-escalated hypofractionated intensity modulated prostate radiation therapy: results from a randomized trial. *International Journal of Radiation Oncology, Biology, Physics* 2014;**88**(5):1074–84.

Ijiri 1990
Ijiri K, Potten C. The circadian rhythm for the number and sensitivity of radiation-induced apoptosis in the crypts of mouse small intestine. *International Journal of Radiation Biology* 1990;**58**(1):165–75.

Kalaiselvan 2014
Kalaiselvan R, Theis VS, Dibb M, Teubner A, Anderson ID, Shaffer JL, et al. Radiation enteritis leading to intestinal failure: 1994 patient-years of experience in a national referral centre. *European Journal of Clinical Nutrition* 2014; **68**:166–70.

Khalid 2006
Khalid U, McGough C, Hackett C, Blake P, Harrington KJ, Khoo VS, et al. A modified inflammatory bowel disease questionnaire and the Vaizey Incontinence questionnaire are more sensitive measures of acute gastrointestinal toxicity during pelvic radiotherapy than RTOG grading. *International Journal of Radiation Oncology, Biology, Physics* 2006;**64**(5):1432–41.

Kilic 2001
Kilic D, Ozenirler S, Egehan I, Dursun A. Sulfasalazine decreases acute gastrointestinal complications due to pelvic radiotherapy. *Annals of Pharmacotherapy* 2001;**35**(7-8): 806–10.

Kligler 2008
Kligler B, Cohrsson A. Probiotics. *Family Physician* 2008; **78**(9):1073–8.

Koontz 2015
Koontz BF, Bossi A, Cozzarini C, Wiegel T, D'Amico A. A systematic review of hypofractionation for primary management of prostate cancer. *European Urology* 2015;**68** (4):683–91.

Kouvaris 2007
Kouvaris JR, Kouloulias VE, Vlahos LJ. Amifostine: the first selective-target and broad-spectrum radioprotector. *Oncologist* 2007;**12**(6):738–47.

Krol 2014
Krol R, Smeenk RJ, Van Lin EN, Yeoh EE, Hopman WP. Systematic review: anal and rectal changes after radiotherapy for prostate cancer. *International Journal of Colorectal Disease* 2014;**29**(3):273–83.

Lischalk 2016
Lischalk JW, Kaplan ID, Collins SP. Stereotactic body radiation therapy for localized prostate cancer. *Cancer Journal* 2016;**22**(4):307–13.

Michalski 2010
Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *International Journal of Radiattion Oncology, Biology, Physics* 2010;**76**(3 Suppl):S123–9.

Moon 2017
Moon DH, Efstathiou JA, Chen RC. What is the best way to radiate the prostate in 2016?. *Urologic Oncology* 2017;**35** (2):59–68. [DOI: 10.1016/j.urolonc.2016.06.002

Morris 2015
Morris KA, Haboubi NY. Pelvic radiation therapy: Between delight and disaster. *World Journal of Gastrointestinal Surgery* 2015;**7**(11):279–88.

Muls 2014
Muls AC. Acta Oncologica Lecture. Gastrointestinal consequences of cancer treatment and the wider context: a bad gut feeling. *Acta Oncologica* 2014;**53**(3):297–306.

NCAT 2012
National Cancer Action Team. National radiotherapy implementation group report: Image guided radiotherapy (IGRT). www.natcansat.nhs.uk%2Fdlhandler.ashx%3Fd%3Dpubs%26f%3DNational%2520Radiotherapy%2520Implementation%2520Group%2520Report%2520IGRT usg=AFQjCNHwVBzIpkFBJ4xyx0uaZqSUZ62KEw& cad=rja (accessed 13 July 2016).

Norkus 2013
Norkus D, Karklelyte A, Engels B, Versmessen H, Griskevicius R, De Ridder M, et al. A randomized hypofractionation dose escalation trial for high risk prostate cancer patients: Interim analysis of acute toxicity and quality of life in 124 patients. *Radiation Oncology* 2013;**8**: 206.

Nout 2010
Nout RA, Smit VT, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet* 2010;**375**(9719):816–23.

O'Brien 2002
O'Brien PC, Franklin CI, Poulsen MG, Joseph DJ, Spry NS, Denham JW. Acute symptoms, not rectally administered sucralfate, predict for late radiation proctitis: longer term follow-up of a phase III trial - Trans-Tasman Radiation Oncology Group. *International Journal of Radiation Oncology, Biology, Physics* 2002;**54**(2):442–9.

Olopade 2005
Olopade FA, Norman A, Blake P, Dearnaley DP, Harrington KJ, Khoo V, et al. A modified Inflammatory Bowel Disease questionnaire and the Vaizey Incontinence questionnaire are simple ways to identify patients with significant gastrointestinal symptoms after pelvic radiotherapy. *British Journal of Cancer* 2005;**92**(9):1663–70.

Pollack 2013
Pollack A, Walker G, Horwitz EM, Price R, Feigenberg S, Konski A, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *Journal of Clinical Oncology* 2013;**31**(31):3860–8.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rodier 1991
Rodier J, Janser J, Rodier D, Dauplar J, Kauffmann P, Le Bouedec G, et al. Prevention of radiation enteritis by an absorbable polyglycolic acid mesh sling. A 60-case multicentric study. *Cancer* 1991;**68**(12):2545–9.

Schünemann 2011
Schünemann HJ, Oxman AD, Vist GE, Higgins JP, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Shadad 2013
Shadad AK, Sullivan FJ, Martin JD, Egan LJ. Gastrointestinal radiation injury: prevention and treatment. *World Journal of Gastroenterology* 2013;**19**(2):199–208.

Soh 2015
Soh FY, James ML, Hickey BE, Daly T, Jeffery M, See AM, et al. Altered radiation fractionation schedules for clinically localised and locally advanced prostate cancer. *Cochrane Database of Systematic Reviews* 2015, Issue 1. [DOI: 10.1002/14651858.CD011462

Sorbe 2012
Sorbe B, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B. External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma - A prospective randomized study. *International Journal of Radiation Oncology, Biology, Physics* 2012;**82**(3):1249–55.

Stacey 2014
Stacey R, Green JT. Radiation-induced small bowel disease: latest developments and clinical guidance. *Therapeutic Advances in Chronic Disease* 2014;**5**(1):15–29.

Theis 2010
Theis V, Sripadam R, Ramani V, Lal S. Chronic radiation enteritis. *Clinical Oncology* 2010;**22**(1):70–83.

Van de Wetering 2013
Van de Wetering FT, Heus P, Verleye L, Van Tienhoven G, Scholten RJ. Probiotics for the prevention or treatment of chemotherapy or radiotherapy related diarrhoea in cancer patients. *Cochrane Database of Systematic Reviews* 2013, Issue 12. [DOI: 10.1002/14651858.CD008831.pub2

Van de Wetering 2016
Van de Wetering FT, Verleye L, Andreyev HJ, Maher J, Vlayen J, Pieters BR, et al. Non-surgical interventions for late rectal problems (proctopathy) of radiotherapy in people who have received radiotherapy to the pelvis. *Cochrane Database of Systematic Reviews* 2016, Issue 4. [DOI: 10.1002/14651858.CD003455.pub2

Wachter 2000
Wachter S, Gerstner N, Goldner G, Pötzi R, Wambersie A, Pötter R. Endoscopic scoring of late rectal mucosal damage

after conformal radiotherapy for prostatic carcinoma. *Radiotherapy and Oncology* 2000;**54**(1):11–9.

Wang 2007
Wang J, Boerma M, Fu Q, Kulkarni A, Fink LM, Hauer-Jensen M. Simvastatin ameliorates radiation enteropathy development after localized, fractionated irradiation by a protein C-independent mechanism. *International Journal of Radiation Oncology, Biology, Physics* 2007;**68**(5):1483–90.

Wedlake 2013
Wedlake LJ, Shaw C, Whelan K, Andreyev HJ. Systematic review: the efficacy of nutritional interventions to counteract acute gastrointestinal toxicity during therapeutic pelvic radiotherapy. *Alimentary Pharmacology & Therapeutics* 2013;**37**(11):1046–56.

Weisendanger-Wittmer 2012
Wiesendanger-Wittmer EM, Sijtsema NM, Muijs CT, Beukema JC. Systematic review of the role of a belly board device in radiotherapy delivery in patients with pelvic malignancies. *Radiotherapy and Oncology* 2012;**102**(3): 325–34.

Yavuz 2002
Yavuz MN, Yavuz AA, Aydin F, Can G, Kavgaci H. The efficacy of octreotide in the therapy of acute radiation-induced diarrhea: a randomized controlled study. *International Journal of Radiation Oncology, Biology, Physics* 2002;**54**(1):195–202.

Yu 2016
Yu T, Zhang Q, Zheng T, Shi H, Liu Y, Feng S, et al. The effectiveness of intensity modulated radiation therapy versus three-dimensional radiation therapy in prostate cancer: a meta-analysis of the literatures. *PLoS One* 2016;**11**(5): e0154499.

References to other published versions of this review

Lawrie 2017
Lawrie TA, Green JT, Beresford M, Burden S, Lal S, Davidson SE, et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy. *Cochrane Database of Systematic Reviews* 2017, Issue 2. [DOI: 10.1002/14651858.CD012529

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmad 2010

Methods	Design: Double-blind, randomised, placebo-controlled clinical trial Country: USA Accrual dates: November 2002 to September 2006 Trial Reg.: NR Funding source: Brent Flickinger (Archer Daniels Midland, Decatur, IL) for providing the soy isoflavone and placebo tablets for the study
Participants	No. randomised: 42 Inclusion criteria: Patients with histologically proven, localised prostate cancer who were scheduled to receive curative radiation therapy were eligible to participate in the study. Eligible patients had to be 18 yrs or older with an ECOG performance status of 3 or less Exclusion criteria: Patients could not have been treated with previous or concurrent hormone therapy or chemotherapy. Patients were not allowed to take concurrent vitamins, herbs, or micronutrients while they were in the study; but if they wished, they could take a single multivitamin daily Gender: Male Age: Intervention: 60, Control: 65 Type of cancer: Prostate Radiotherapy regimen received: 73.8 Gy - 77.5 Gy in 1.8 to 2.5 Gy fractions Primary/adjuvant/other: Primary Other treatment received: Patients excluded if on previous/concurrent HT or CT
Interventions	Comparison: Soy isoflavone vs placebo Arm 1: Participants had to take 2 50-mg soy isoflavones (Novasoy) tablets twice daily (it could be taken in 1 dose or 2 divided doses with meals). Participants were instructed to take 2 tablets with breakfast and 2 tablets with dinner beginning with the first day of radiation Participants were instructed to continue to take the study tablets for 6 months in the absence of unacceptable toxicity Arm 2: Identical-looking placebo tablets
Outcomes	GI toxicity: Acute and late NCI CTC (EPIC?) QoL: QOL questionnaire (50 questions at 3 months or 53 questions at 6 months) Other review outcomes: Despite repeated reminders, only 26 participants returned their 3-month and 6-month QOL questionnaires. Group 1 had 13 questionnaires returned for 3-month and 6-month evaluations, and Group 2 had 13 questionnaires returned for 3-month visits and 14 questionnaires for 6-month visits. Further data analysis was restricted to those who returned their questionnaires Other study outcomes: NR Duration of follow-up: 6 months
Notes	Compliance was 100% with the study tablets. However, only 62% of the participants returned the study questionnaires. Therefore, no attempt was made at statistical analysis, which would be meaningless given the very small number of events in each study arm. This study should be considered hypothesis-generating rather than hypothesis-testing

Ahmad 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 42 patients who were enrolled, only 26 completed the study endpoints at 3 and 6 months (38% attrition)
Selective reporting (reporting bias)	High risk	The QoL questionnaire used is not named (It sounds as if it is the EPIC questionnaire) . An assessment was completed at the end of RT but the results of this time point are not reported. Percentage of participants experiencing any genitourinary, gastrointestinal or sexual function side effects are reported but there is no indication of severity
Other bias	Unclear risk	It seems as if 8 participants in each arm did not return questionnaires at 3m and 6m but their characteristics are not provided
Overall judgement	High risk	This was a small study, not statistically powered to a primary end point and with a very high rate of attrition

Arafat 2016

Methods	Design: RCT Country: Egypt Trial Reg.: NR Funding source: NR
Participants	No. randomised: 60 Inclusion criteria: Operative muscle-invasive transitional cell bladder cancer, WHO performance status 2 or less, able to tolerate chemoradiation, adequately functioning bladder, within 8 weeks or TURB, normal organ functioning, written informed consent Exclusion criteria: Hydronephrosis, metastases, pregnancy, systemic disease, inflamma-

	tory bowel disease, nephrotoxic or ototoxic drugs, not a candidate for radical systectomy, other malignancy within 2 years Gender: 90% male, 10% female Age: 68.3% of participants were 55 and older, age distribution similar between groups Type of cancer: Bladder Radiotherapy regimen received: 64 Gy in standard fractions Primary/adjuvant/other: Adjuvant Other treatment received: Concurrent and adjuvant paclitaxel/cisplatin chemotherapy
Interventions	Comparison: Reduced dose volume versus standard dose volume Arm 1: 64 Gy whole bladder radiotherapy alone in 3-field technique Arm 2: Standard treatment (44 Gy whole pelvis radiotherapy in 4-field technique followed by 20 Gy bladder boost)
Outcomes	GI toxicity: acute and late (EORTC/RTOG) QoL: NR Other review outcomes: NR Other study outcomes: survival, loco-regional relapse and metastases Duration of follow-up: 2 years
Notes	Baseline characteristics were comparable, including age, tumour stage, gender, extent of resection, performance status, bilharzial status, tumour site, size, multiplicity, and presenting symptoms. GI toxicity was described as 'mostly in the form of diarrhoea and rectal pain' but the incidence of specific symptoms was not quantified. Investigators concluded that irradiating the bladder only significantly decreased acute radiation toxicity, not late toxicity

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement: "60 patients were randomised into two treatment groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Acute and late toxicity reported on 47/60 participants (24 and 23 respectively), reasons for attrition not clearly stated

Arafat 2016 (*Continued*)

Selective reporting (reporting bias)	Low risk	Expected outcomes reported (protocol not seen)
Other bias	Low risk	Baseline characteristics comparable between groups
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Arregui Lopez 2012

Methods	Design: RCT Country: NR Accrual dates: November 2010 to May 2011 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 29 Inclusion criteria: NR Exclusion criteria: NR Gender: NR Age: NR Type of cancer: Rectal adenocarcinoma Radiotherapy regimen received: Median dose 45 Gy Primary/adjuvant/other: Primary Other treatment received: Concomitant preoperative capecitabine
Interventions	Comparison: steady diet (not defined) versus an exclusion diet (not defined) based on general recommendations Arm 1: A "steady diet", intervention period not specified but presumed to be at least during RT Arm 2: Control group, participants advised a diet based on exclusion
Outcomes	GI toxicity: Acute CTCAE v 2.0 scale QoL: Validated FACIT-D questionnaire Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT and 3 weeks post-RT
Notes	At the end of the treatment, the control group lost 2.12 kg and the steady diet group gained 1.41 kg (P = 0.001)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement

Arregui Lopez 2012 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	29 patients were randomised and data from 29 are presented in the abstract
Selective reporting (reporting bias)	Unclear risk	Protocol not seen and few expected outcomes were reported
Other bias	High risk	Nature of intervention not defined, compliance wth intervention not reported. No powering statement provided. No baseline details reported, so groups may have been unbalanced at start. Intervention not clearly described
Overall judgement	High risk	Due to methodological limitations above

Athanassiou 2003

Methods	Design: Phase III, multicentric, randomised trial Country: Greece Accrual dates: January 1999 to September 2000 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 205 Inclusion criteria: Histologically-proven carcinoma of the rectum, bladder, prostate, or gynaecologic tract, with no evidence of metastatic disease. Patients were referred for radical or postoperative RT of the primary tumour. The eligibility criteria were age 18 - 70 years, Karnofsky performance status 60, and life expectancy 6 months, normal renal and liver function, a leukocyte count 3000/mm^3, haemoglobin level 9 g/dL, and a platelet count 100,000/mm^3. Participants were required to give written informed consent Exclusion criteria: Patients with prior RT to the pelvis or chemotherapy within 4 weeks of the initiation of RT were excluded. Clinically-evident pulmonary insufficiency, major heart disease, and history of cardiac infarction that occurred 6 months before entry into the study Gender: 47.8% male Age: Intervention: 63.8 (mean), Control: 64.7 (mean) Type of cancer: Rectal (32); bladder (47); prostate (40); gynaecologic tumours (86) Radiotherapy regimen received: 50 Gy to 70 Gy standard fractionation Primary/adjuvant/other: Primary and adjuvant Other treatment received: NR

Athanassiou 2003 (*Continued*)

Interventions	Comparison: amifostine vs control Arm 1: Amifostine 340 mg/m^2 was administered during 3 - 5 mins by i.v. infusion, daily, 15 - 30 mins before RT Arm 2: RT alone (control)
Outcomes	GI toxicity: Acute and late CTC v2.0 EORTC/RTOG QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: A mean of 12 months.
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	High risk	Unclear reporting of side effects related to amifostine and late follow-up data. Percentages presented without denominators
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	High risk	Due to methodological and reporting limitations

Baughan 1993

Methods	Design: Double-blind RCT Country: United Kingdom Accrual dates: NR Trial Reg.: NR Funding source: NR
Participants	No. randomised:74 (73 analysed) Inclusion criteria: Any patient due to receive radical pelvic radiotherapy Exclusion criteria: Renal failure, pre-existing colitis, sensitivity to salicylates Gender: NR Age: NR Type of cancer: Gastrointestinal (4/72), urological (55/72), gynaecological (15/72) Radiotherapy regimen received: Varied between 30 to 60 Gy over 3 to 7 weeks (similar distribution between intervention and control group) Primary/adjuvant/other: NR Other treatment received: NR
Interventions	Comparison: 5-ASA vs placebo Arm 1: 800 mg 5-aminosalicylic acid (5-ASA) 3 times a day, commencing before RT and continuing for 4 weeks after Arm 2: Identical-looking placebo
Outcomes	GI toxicity: Acute and late (unvalidated scale) QoL: NR Other review outcomes: Medication for symptom control Other study outcomes: None Duration of follow-up: 1 year
Notes	Baseline characteristics reported included RT dose and bowel symptoms before RT, which were comparable between study arms

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A double-blind randomization was performed centrally using a computer generated randomisation table"
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" with "identical-looking placebo"
Blinding of outcome assessment	Low risk	Participant-reported outcomes with "double-blind" randomisation and "identical-looking placebo"

Baughan 1993 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant in the 5-ASA group died 3 days after starting RT and was "considered unevaluable"
Selective reporting (reporting bias)	Low risk	Protocol not seen but expected outcomes were reported; study findings were negative
Other bias	Low risk	None noted
Overall judgement	Low risk	

Botten 2015

Methods	Design: RCT Country: NR Accrual dates: NR Trial Reg.: NR Funding source: NR
Participants	No. randomised: 43 Inclusion criteria: NR Exclusion criteria: NR Gender: Male Age: reported as 72 (52 - 84) years Type of cancer: Prostate Radiotherapy regimen received: NR Primary/adjuvant/other: NR Other treatment received: NR
Interventions	Comparison: ERB vs no ERB Arm 1: Daily insertion of an endorectal balloon (ERB) during IGRT Arm 2: No ERB during IGRT
Outcomes	GI toxicity: acute (1 month) and late (1 year) (LENT-SOMA) QoL: EORTC QLQ -C30 and QLQ-PR25 Other review outcomes: NR Other study outcomes: Urinary toxicity and measures of anorectal function (motor and sensory) and rectal compliance at 1 year Duration of follow-up: 1 year
Notes	Baseline characteristics were not described in the conference abstract A greater proportion of IGRT+ERB participants had QLQ-PR25 disease-specific urinary symptoms Authors reported that "IGRT+ERB reduces GI symptoms, rectal sensitivity and the impairment of health-related QoL outcomes at the expense of increased urinary symptoms"

Risk of bias

Botten 2015 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only. Insufficient details to make judgement
Allocation concealment (selection bias)	Unclear risk	Abstract only. Insufficient details to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Abstract only. Insufficient details to make judgement
Blinding of outcome assessment	Unclear risk	Abstract only. Insufficient details to make judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only. Insufficient details to make judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient details to make judgement; outcome data reported as percentages
Other bias	Unclear risk	At the time of judgement, this study had not been reported in full
Overall judgement	Unclear risk	Abstract only. Insufficient details to make judgement

Chang 2016

Methods	Design: Parallel-arm RCT Country: China Accrual dates: Nov 2009 to Dec 2010 Trial Reg.: NR Funding source: National Natural Science Foundation of China (Nos. 30960439, 81560488, and 81101693) Yunnan Health Scienco and Key Project of Department of Education of Yunnan Province (2015Z090) and the Chinese National Key Clinical Specialty (Oncology) fund
Participants	67 randomised (65 analysed) Inclusion criteria: Women receiving primary RT for non-metastatic cancer of the cervix; patients received no chemotherapeutic drugs within 4 weeks or previous RT on pelvic cavity; leucocyte > 4.0×109/L, neutrophil > 2.0×109/L, platelets > 100×109/L; no significant system dysfunction or serious malnutrition; signed informed consent Exclusion criteria: Women participating or planning to participate in other clinical trials Gender: Female Mean age: 47.5 years Type of cancer: Cervix

	Radiotherapy regimen received: EBRT 50 Gy, 5 - 6 weeks, 25 fractions Primary/adjuvant/other: Primary Other treatment received: External-beam RT (50 Gy, 5 - 6 weeks, 25 fractions) was performed on the participants at different times of the day according to the group under X-ray using Linear Accelerator (Varian 2100C/D, Varian Inc., Palo Alto, CA, USA). 36 - 42 Gy of brachytherapy in 6 - 7 fractions was given to all participants at the same time under γ-ray using after-loading RT unit
Interventions	Arm 1: Morning (9 - 11 am) RT Arm 2: Evening (9 - 11 pm) RT RT regimen was 50 Gy in 25 fractions plus brachytherapy
Outcomes	GI toxicity: Diarrhoea (overall and severe (grade 3 and 4)) Other review outcomes: Nausea/vomiting Other study outcomes: Haematological toxicity Duration of follow-up: NR, but appears to be during RT only
Notes	Authors concluded that "RT at different time intervals results in similar efficacy. However, RT in the morning reduces severe hematological toxicity." This study reported significantly more Grade 3/4 haematological toxicity with evening RT compared with morning RT and little difference in severe diarrhoea

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were prospectively randomised... " - on further details provided
Allocation concealment (selection bias)	Unclear risk	No details are provided on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is not possible to blind participants to this intervention
Blinding of outcome assessment	Low risk	"Acute radiation injuries were assessed weekly with the radiation therapy oncology group (RTOG)'s common toxicity criteria. The observer was blinded to the radiation time of patients."
Incomplete outcome data (attrition bias) All outcomes	High risk	"Two patients were excluded from the enrolled patients because of treatment-related complications during the treatment". It is not stated to which groups these participants were allocated

Chang 2016 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	"Hematological toxicity, intestinal mucositis, diarrhea, nausea, and vomiting were included." However, only haematological and diarrhoea data are reported
Other bias	Unclear risk	Power calculation does not appear to have been performed and study is most likely underpowered
Overall judgement	Unclear risk	Mainly due to lack of methodological details

Chary 1984

Methods	Design: Prospective randomised double-blind trial Country: Canada Accrual dates: NR Trial Reg: NR Funding source: Dr. J. E. Knapp, Bristol-Myers Pharmaceuticals supplied medicatication. Other information unclear from scan of document
Participants	No. randomised: 35 (33 analysed) Inclusion criteria: Patients with the primary diagnosis of carcinoma of cervix, body of uterus or ovary (gynaecological) and carcinoma of prostate (urological) with a performance status of 0 to 1 ECOG scale Exclusion criteria: Patients with pre-existing gastrointestinal problems who had undergone intestinal surgery, colostomy and previous chemotheraphy or RT. Sensitivity to cholestyramine or receiving anticoagulant therapy Gender: 69.69% male Age mean (SD): Intervention: 67.9 (7.1), Control: 68.1 (6.8) Type of cancer: Bladder (12/33), prostate (11/33), cervix (4/33), ovary (3/33), endometrium (3/33) Radiotherapy regimen received: Single daily dose not exceeding 200 cGy, total dose given as 5 fractions each week over 5 to 6 weeks Primary/adjuvant/other: Primary Other treatment received: All participants started a 40 gm fat diet
Interventions	Control: Cholestyramine vs placebo Arm 1: Cholestyramine 4 gm twice a day orally Arm 2: Placebo given in powder form 4 gm twice a day
Outcomes	GI toxicity: Acute Ungraded QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT and up to 2 months post-RT
Notes	None

Chary 1984 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Low risk	"Following the termination of the trial code for test medication was broken"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"In both groups the compliance was good"
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Chitapanarux 2010

Methods	Design: Prospective, randomised, double-blind, placebo-controlled study Country: Thailand Accrual dates: January 2007 to April 2009 Trial Reg.: NR Funding source: The medication package was provided by the sponser
Participants	No. randomised: 63 Inclusion criteria: Patients aged at least 18 and not more than 65 years old, with FIGO stage IIB - IIIB squamous cell carcinoma of cervix, who were planned to receive the standard treatment for locally-advanced cervical cancer of external beam whole pelvis radiotherapy and brachytherapy plus weekly cisplatin 40 mg/m^2, with ECOG performance status 0 - 1 and negative anti-HIV were included Exclusion criteria: Past history of pelvic radiotherapy or abdominal surgery and diarrhoea before the beginning of this study. Patients who had any gastrointestinal disease, were pregnant and lactating were also excluded from the study Gender: Female Age: Intervention: 47 (median), Control: 52 (median) Type of cancer: Cervical Radiotherapy regimen received: 200 cGy per fraction, 5 fractions per week followed by brachytherapy

Chitapanarux 2010 (*Continued*)

	Primary/adjuvant/other: Primary Other treatment received: Participants with cervical cancer received a weekly intravenous dose of cisplatin of 40 mg/m^2 during external beam RT
Interventions	Comparison: lactobacillus acidophilus plus bifidobacterium bifidum vs placebo Arm 1: 2 × 10(9) units of a lactobacillus acidophilus plus bifidobacterium bifidum (equivalent to 2 capsules) twice a day before meals (morning and evening), beginning 7 days before starting RT and continuing every day during RT Arm 2: Identical-appearing placebo
Outcomes	GI toxicity: Acute CTCAE v2.0 QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT (6 weeks?)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised and stratified by age, cancer stage and pelvic RT technique. Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were randomised and stratified by age, cancer stage and pelvic RT technique. Method of randomisation not stated
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study protocol
Selective reporting (reporting bias)	Low risk	Study outcomes as stated were all reported
Other bias	Unclear risk	Although a sample size calculation (29 per group) is provided, the difference sought in the primary end point between groups (i.e. incidence of Grade ≥ 2 diarrhoea/need for rescue medication) is not specified
Overall judgement	Unclear risk	Unclear, based on methodological limitations above

Chopra 2015

Methods	Design: Phase III open, parallel-arm RCT Country: India Trial Reg.: NCT 01279135 Accrual dates: 2011 - ongoing Funding source: Funded at Tata Memorial Centre by Department of Atomic Energy Clinical Trials Unit and Government Agency grant-DAECTC grant for TMC IRB 803
Participants	No. randomised: Interim analysis = 120 (240 accrual planned) Inclusion criteria: Women > 18 years of age who had undergone surgery for cervical cancer and who needed adjuvant (chemo) radiation Exclusion criteria: Women with residual pelvic or para-aortic nodal disease, history of multiple abdominal surgeries or any other medical bowel condition Gender: Female Type of cancer: Cervix Primary RT/adjuvant RT/other: Adjuvant Other treatment received: Some received concurrent platinum-based chemotherapy (cisplatin 40mg/m^2) if indicated. All participants received VBT (6 Gy) after EBRT
Interventions	Comparison: IMRT vs 3DCRT Arm 1: IMRT (50Gy/25 fractions delivered over 5 weeks; PTV 50 Gy: 95% of PTV should receive 95% of the prescription dose; small bowel doses should be reduced as low as possible. All attempts should be made to keep small bowel V15 < 200 cc and V40 Gy < 100 cc. Less than 60% of rectal volume should receive ≥ 30 Gy and < 35% of bladder should receive ≥ 45 Gy; < 15% of the femoral head should receive 30 Gy Arm 2: 3DCRT (50Gy/25 fractions delivered over 5 weeks; conformal 4-field box technique; optional field shaping using blocks or multileaf collimators). The field should conform to the PTV 50 Gy contours with 7 mm margin for multileaf collimator leaves/blocks Both groups treated with a full bladder
Outcomes	GI Toxicity: acute and late (CTCAE v 3) QoL: EORTC QLQC30 and Cx-24 Other review outcomes: NR Other study outcomes: none Duration of follow-up: 3-monthly for 2 years, then 6-monthly
Notes	Primary outcomes to be reported at a median follow-up of 3 years (2019/2020). Interim analysis was reported when 120 participants had completed median follow-up of 20 months (2 - 46) Author reply received 17 January 2017 confirmed typo in abstract - i.e. there should be a ≥ symbol instead of a < symbol. Advised that final analysis will be completed in 2019/20

Risk of bias

Bias	Authors' judgement	Support for judgement

Chopra 2015 (*Continued*)

Random sequence generation (selection bias)	Low risk	"permuted block stratified randomisation"; "All randomisation will be done centrally through Epidemiology and Clinical Trials Unit at Advanced Centre for Treatment Research and Education in Cancer (ACTREC)." Stratified according to type of hysterectomy (Wertheim's or simple) and use of chemotherapy
Allocation concealment (selection bias)	Unclear risk	"All randomisation will be done centrally through Epidemiology and Clinical Trials Unit at Advanced Centre for Treatment Research and Education in Cancer (ACTREC)."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open label RCT
Blinding of outcome assessment	Unclear risk	Breaking the randomisation code and outcome assessor blinding is not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 women withdrew consent after randomisation (2 in the 3DCRT arm and 1 in the IMRT arm) and did not receive any treatment and there was 1 protocol deviation in each arm
Selective reporting (reporting bias)	Unclear risk	Unclear, as this report is an interim report (conference abstract only)
Other bias	Unclear risk	Unclear, as this report is an interim report (conference abstract only)
Overall judgement	Unclear risk	Unclear, as this report is an interim report (conference abstract only)

Dale 2001

Methods	Design: A prospective, randomised, open, clinical trial Country: India Accrual dates: October 1996 to September 1997 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 120 Inclusion criteria: Patients with locally-advanced, biopsy-proven carcinomas of the uterine cervix

Dale 2001 (*Continued*)

	Exclusion criteria: Previous history of radiation therapy, chemotheraphy or surgery, and those with WHO performance index below 70% or with uncontrolled systemic diseases were excluded from the study Gender: Female Age: Intervention: 49.9, Control: 49.3 Type of cancer: Uterine cervix Radiotherapy regimen received: 50 - 60 Gy fractionated, followed by 20 - 30 Gy brachytherapy Primary RT/adjuvant RT/other: Primary Other treatment received: Any use of anti-inflammatories, topical anaesthetics, or mucoprotectants for radiation toxicity and concomitant medication, e.g. anti-emetics and anti-diarrhoeal drugs was recorded
Interventions	Comparison: Enzyme vs no intervention Arm 1: 3 tablets 4 times a day, beginning 7 days before start of RT. Enzyme therapy continued for 9 weeks thereafter. 1 enteric coated tablet of the test drug Wobe-Mugis E contains 100 mg papain, 40 mg trypsin and 40 mg chymotrypsin Arm 2: RT only
Outcomes	GI Toxicity: Acute, RTOG/EORTC QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During and at 6 weeks and 3 months after RT ended
Notes	NR

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Authors state that randomisation was done by computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Method of concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	pen-label trial, thus participants unblinded to intervention
Blinding of outcome assessment	High risk	Not clear whether assessors were unblinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/60 participants in the enzyme group withdrew from the trial - reasons unrelated to the intervention
Selective reporting (reporting bias)	Low risk	All prespecified outcomes are reported

Dale 2001 (*Continued*)

Other bias	Low risk	Groups well matched for age, performance status and disease stage at baseline
Overall judgement	High risk	This was an open-label study. No powering statement is provided and the primary end point was not specified

De Maria 1992

Methods	Design: Randomised pilot study Country: Italy Accrual dates: NR Trial Reg.: NR Funding source: NR
Participants	No. randomised: 45 Inclusion criteria: Previously operated on for endometrial cancer and given adjuvant RT, life expectancy > 4 months and informed consent Exclusion criteria: > 70 years old, with diverticulosis, diabetes, serum cretine > 1.5 mg%, or with transaminases, gamma-GT and alkaline phospatase more than 2-fold normal values Gender: Female Age: Intervention: 63.62 (mean), Control: 57.71 (mean) Type of cancer: Endometrial Radiotherapy regimen received: 50 Gy standard fractionation Primary/adjuvant/other: Adjuvant Other treatment received: NR
Interventions	Comparison: Glutathione vs control Arm 1: 1200 mg GSH diluted in 250 mg normal saline solution, i.v., 15 mins before RT Arm 2: 250 mg normal saline solution, i.v., 15 min before RT
Outcomes	GI toxicity: NR QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During and until to 10 days after RT
Notes	RT discontinued in 47% of controls and 28% of GSH-treated participants, reason NR

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement

De Maria 1992 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Three patients could not be evaluated: 1 patient from Group 1 who received vaginal brachytherapy prior to transcutaneous radiotherapy, and 2 patients from Group 2 who were lost to follow-up"
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	RT discontinued in 47% of controls and 28% of GSH-treated participants, reason not reported
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Dearnaley 1999

Methods	Design: Open-label parallel-arm RCT Country: UK Trial Reg.: NR Accrual dates: All participants were treated between 1988 and 1995 Funding source: Cancer Research Campaign programme grant, the Bob Champion Cancer Trust, and the NHS Executive
Participants	No. randomised: 225 Inclusion criteria: Histologically-confirmed prostate cancer at clinical stages T1 - 4, G1 - G3, N0 or M0 (life expectancy judged to be in excess of 5 - 10 years) Exclusion criteria: NR Gender: NR Median age: Intervention: 68 (50 to 83) and Control: 69 (51 to 80) Type of cancer: Prostate Primary RT/adjuvant RT/other: Primary Other treatment received: An initial 3 - 6-month course in androgen deprivation with a LHRH analogue was given to 154 men and was discontinued after RT was completed
Interventions	Comparison: 3DCRT vs ConRT Arm 1: 3DCRT: Total dose of 60 - 64 GY in 2 Gy fractions 5 times a week. Used customised cerrobend blocks to shape the radiation beams with a 6 mm margin around the beam's eye-view projection of the PTV Arm 2: ConRT: Total dose of 60 - 64 GY in 2 Gy fractions 5 times a week with standard rectangular radiation field

Dearnaley 1999 (*Continued*)

	Total dose of 60 - 64 GY in 2 Gy fractions for both arms. Delivered in a 3-field technique
Outcomes	GI Toxicity: Acute and late (RTOG) QoL: NR Other review outcomes: NR Other study outcomes: Biochemical control, survival and other toxicity Duration of follow-up: Every 6 months for 2 years
Notes	Baseline (age, tumour stage and grade, comorbidity) and treatment characteristics (androgen deprivation, radiation dose received, radiation field area) were comparable between groups, except that baseline serum PSA levels were higher in the conRT group (P = 0.04). Overall survival and local control at 2 and 5 years were similar in the 2 treatment groups. A difference in biochemical control was 'not significant' when patients were stratified according to their baseline PSA level

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomised permuted blocks design from an independent randomisation service offered by the Clinical Trials and Statistics Unit, Institute of Cancer Research"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	"unblinded"
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	210 participants had complete RTOG data at 1-year follow-up, (106 conformal, 104 conventional), and 193 (86%) had complete data at 2 years (99 comformal, 94 conventional)
Selective reporting (reporting bias)	Low risk	Expected outcomes reported but protocol not seen
Other bias	Low risk	Serum PSA at baseline differed between the study arms but this is unlikely to have influenced toxicity grades
Overall judgement	Low risk	Good-quality RCT

Delia 2007

Methods	Design: Double-blind, placebo-controlled RCT Country: Italy Accrual dates: May 1999 to December 2005 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 490 Inclusion criteria: No contraindication for probiotic or antibiotic therapy or radiation therapy Exclusion criteria: Patients with a Karnofsky performance score ≤ 70, a life expectancy ≤ 1 year, persistent vomiting or diarrhoea, fistulising disease, known Crohn's disease or ulcerative colitis, intra-abdominal abscesses or fever (> 37.5° C) at the time of enrolment, or clinical, microbiological, or imaging evidence of sepsis syndrome, and requirement for continuous antibiotic treatment or use of antibiotics in the last 2 wks before initiation of VSL#3 therapy Gender: NR Age: NR Type of cancer: Sigmoid, rectal, cervical Radiotherapy regimen received: 60 Gy to 70 Gy fractionated Primary/adjuvant/other: Primary Other treatment received: NR
Interventions	Comparison: probiotic vs placebo Arm 1: VSL#3 (VSL Pharmaceuticals, Fort Lauderdale, MD), 1 sachet 3 times a day., starting from the first day of RT until the end of the scheduled cycles of radiation therapy Arm 2: VSL#3-identical-appearing placebo
Outcomes	GI toxicity: Acute WHO - Gastrointestinal Toxicity QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT and then for 1 month after completion of RT
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement

Delia 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	High risk	Toxicity severity is not graded. Method of assessments are not fully reported. No powering statement or predefined primary outcome is provided
Other bias	High risk	Baseline characteristics are only given for the initial 190 participants recruited (2002 article)
Overall judgement	High risk	Recruitment took over 5 years. Radiotherapy techniques have changed in the 10 years since the 2007 article was published and certainly since the 'box' technique described in the 2002 article

Demers 2014

Methods	Design: Randomised double-blind controlled trial Country: Canada Accrual dates: December 2006 to September 2010 Trial Reg.: NR Funding source: Virage Santé provided probiotic and placebo
Participants	No. randomised: 246 (229 analysed) Inclusion criteria: Patients included were over 18 years old with ECOG performance status of 0 or 1. They had a pelvic cancer (gynaecologic, rectal, or prostate) for which they were to receive RT treatments for a minimum of 40 Gy at the pelvic level, with or without chemotherapy at University Health Center, L'Hôtel-Dieu de Québec (UHC-HDQ) Exclusion criteria: Previous RT treatment in the pelvic or abdominal region, medical history of gastro-intestinal inflammation, malabsorption syndrome, inflammatory bowel disease, coeliac disease, ileostomy, daily use of anti-diarrhoeal medication before RT, pregnancy, breastfeeding, neutropenia or probiotic intolerance Gender: 66.81% male Mean age: Intervention 1: 61.4, Intervention 2: 62, Control: 60 Type of cancer: Prostate (75/229), endometrium (26/229), cervix (26/229), rectum (96/229), others (6/229) Radiotherapy regimen received: 40 Gy to 50.4 Gy in standard fractionation Primary/adjuvant/other: Primary and adjuvant Other treatment received: Daily intake of yogurt was suggested
Interventions	Comparision: Probiotic vs placebo Arm 1: Participants received the standard dose at 1.3 billion CFU twice a day. Bifilact! was the probiotic agents used in the study. Each capsule contained maltodextrine and magnesium stearate as excipients. Capsule intake started on the first day and ended on

	the last day of RT treatments. Participants received individualised nutritional advice aimed at reducing lipid intake, avoiding caffeine and alcohol and advice (no dose stated) on the consumption of dietary fibre Arm 2: Participants received the higher dose of 10 billion CFU three times a day. Bifilact! was the probiotic agents used in the study. Each capsule contained maltodextrine and magnesium stearate as excipients. Capsule intake started on the first day and ended on the last day of RT. Participants received individualised nutritional advice aimed at reducing lipid intake, avoiding caffeine and alcohol and advice (no dose stated) on the consumption of dietary fibre Arm 3: Participants received placebo
Outcomes	GI toxicity: Acute WHO scale QoL: EORTC-QLQ-C30 Other review outcomes: NR Other study outcomes: Secondary objectives were to assess whether intake of Bifilact! decreased or delayed the need of anti-diarrhoeal medication as well as reducing intestinal pain, decreasing need for hospitalisation, lowering the interruption of radiotherapy treatments or doses of both radiotherapy or chemotherapy, and finally, to assess whether the overall well-being of participants was improved during treatment Duration of follow-up: Maximum duration of follow up was 10 weeks
Notes	The high-dose probiotic group was introduced following an interim analysis which revealed a reduction in maximum-grade diarrhoeal toxicity in the probiotic arm. New random lists were generated (ratio 3:1:1 - high dose: standard dose: placebo) but the study was not repowered to take account of the additional group/comparisons. Subgroup analysis revealed that in participants who had had prior surgery, the group receiving the standard probiotic dose had fewer participants experiencing severe diarrhoea (74%) compared to the placebo group (97%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation using permuted blocks, stratified by cancer site and receipt or not of chemotherapy
Allocation concealment (selection bias)	Low risk	The method of concealments is described as coded bottles with only the dispensing nurse having access to the code
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded to intervention. Study personnel including the dietitian and other 'care-givers' blinded to intervention
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement

Demers 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates between first and last assessments in all intervention groups were < 11%
Selective reporting (reporting bias)	Low risk	All prespecified outcomes are reported
Other bias	Unclear risk	Participants were allowed to consume yoghurt products containing live bacteria. However, authors state they wanted to mimic a real-life situation and concentrations of live bacteria in off-the-shelf products may not be as high as in probiotic supplements. All patients received individualised nutritional counselling and compliance with advice was reportedly high. This may have favourably altered symptom severity/incidence, but the effect should have been similar accross all groups
Overall judgement	Unclear risk	Based on methodological concerns above

Emami 2014

Methods	Design: Double-blind, randomised, placebo-controlled study Country: Iran Accrual dates: February 2013 to September 2013 Trial Reg.: IRCT2013052213433N1 Funding source: This study was funded by reseach chancellor of Isfahan University of Medical Sciences as a disseration Project no 1957
Participants	No. randomised: 42 Inclusion criteria: Patients receiving standardised abdomen and pelvic irradiation 5000 cGy (1000 cGy weekly) for prostate, uterus, cervix, bladder, rectum and colon cancers, willing and able to provide written informed consent for study participation were included Exclusion criteria: Past history of irradiation, diarrhoea before beginning of pelvic irradiation were ineligible for the study. Exclusion criteria included occurence of unbearable diarrhoea, taking another drug for treatment of diarrhoea during the study and unwilling to participate in the study at any time Gender: 54.76% male Age: Intervention: 65.7, Control 58.7 Type of cancer: Prostate, uterus, cervix, bladder, rectum and colon Radiotherapy regimen received: 50 Gy in standard fractionation Primary RT/adjuvant RT/other: Primary and adjuvant Other treatment received: Some participants received concomitant chemotherapy

Interventions	Comparison: Green tea vs placebo Arm 1: 1 tablet daily of 450 mg green tea (Camgreen, Iran Giahessence Pharmancy Co.) for 5 weeks Arm 2: Identical-looking placebo (Isfahan Farabi Pharmacy Co.)
Outcomes	GI Toxicity: Acute, CTC NCI verion 3.0, functional living index emesis QoL: Functional Living Index Other review outcomes: NR Other study outcomes: NR Duration of follow-up: Weekly for 4 weeks
Notes	Authors note that, in Asia, green tea has been used to treat diarrhoea historically and is still used for this purpose Diarrhoea (grade 1 or more) occurred more commonly in the placebo group of this study (but was not statistically significant). Reported findings included an increase in severity of diarrhoea (diarrhoea scores) in the placebo group during RT, but not in the green tea group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Study was randomised although method of randomisation is not stated
Allocation concealment (selection bias)	Low risk	Randomisation code only known to the database programmer
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and study assessors blinded to intervention
Blinding of outcome assessment	Low risk	Study assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 21 participants in each group returned evaluable data
Selective reporting (reporting bias)	High risk	The primary end point (difference beween groups in the need for anti-diarrhoeal medication) is not reported. Self-reported outcomes (stool frequency, consistency) and intestinal cramps are not reported
Other bias	Low risk	Some imbalance in baseline characteristics but these are not extreme or significant. Age 65.7 (Int 1) vs 58.7 (Placebo) P = 0. 06 and women comprise 12/21 (Int 1) vs 7/21 (Placebo) P = 0.09

Emami 2014 (*Continued*)

Overall judgement	High risk	Powered on a difference between groups in the need for anti-diarrhoeal medication of 32% (placebo) vs 9% (Intervention 1) . However, these figures based on a 1983 publication so will not necessarily reflect toxicity experienced using more up-to-date techniques. Study may have been under-powered to detect the difference sought, which was not demonstrated

Esco 2004

Methods	Design: Randomised, controlled, open-label, Phase IV clinical trial Country: Spain Accrual dates: August 1997 to March 2000 Trial Reg.: NR Funding source: Tedec-Meiji Farma, SA supported stastistical analysis of results and manuscript preparation
Participants	No. randomised: 100 Inclusion criteria: > 18 years, diagnosis of rectal cancer, prior surgey for rectal cancer, an indication for pelvic RT. Patients with history of protein hypersensitivity had to have a negative SOD sensitivity skin test result Exclusion criteria: Pregnancy or lactation, expected survival of > 6 months, allergy to the study drug, impaired liver function (serum glutamic-oxaloacetic transaminase/serum glutamic-pyruvic transaminase and bilirubin levels 3x greater than normal upper limit, impaired renal funcion (serum creatine levels > 200 umol/L or 2.3 mg/dL), pathologic conditions related to accelerated copper (Wilson's disease) or zinc metabolism, anti-inflammatory medication during RT or subsequent 7 weeks, inability to comply with follow-up and/or understand study procedures Gender: NR Age: NR Type of cancer: Rectal Radiotherapy regimen received: 50 Gy in standard fractionation Primary/adjuvant/other: Adjuvant Other treatment received: Chemotherapy 3 cycles each before and after RT. Treatment with antibacterial agents and anti-diarrhoeal medication was allowed
Interventions	Comparison: Orgotein vs control Arm 1: 8 mg of orgotein i.m. three times weekly for 7 weeks Arm 2: No treatment (control)
Outcomes	GI toxicity: RTOG QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: Up to 2 years

Esco 2004 (*Continued*)

Notes	Owing to the underlying disease and associated complications, 15 participants died during the study: 7 in the orgotein group (14%), and 8 in the control group (16.4%); this 'made no statistically significant differences'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One patient from the control group was excluded because of concomitant disease and an absence of data subsequent to the inclusion visit"
Selective reporting (reporting bias)	Unclear risk	Protocol not seen and few review outcomes reported
Other bias	Low risk	"Analysis of patient demographic and baseline characteristics did not find any statistically significant differents…" "All tumours were located in the rectum….surgical techniques used were similar in both groups"
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Fuccio 2011

Methods	Design: Double-blind, placebo-controlled, randomised trial Country: Italy Accrual dates: June 2007 to October 2008 Trial Reg.: EudraCT: 2006-005697-46 Funding source: Sofar s.p.a., (Trezzano Rosa, Milan, Italy) provided both the beclomethasone dipropionate and the placebo used in the trial and funded the study logistics
Participants	No. randomised: 120 Inclusion criteria: Histological proof of prostate cancer without distant metastases, undergoing a course of external beam radiation therapy Exclusion criteria: Known allergy to beclomethasone dipropionate, a history of inflam-

	matory bowel disease, active malignant intraluminal gastrointestinal tumours or active inflammatory process (i.e. diverticulitis, inflammatory bowel disease), a previous history of pelvic radiotherapy or previous colorectal surgery Gender: Male Age: Intervention: 70.9 ± 6 (mean), Control: 69.5 ± 6.2 (mean) Type of cancer: Prostate Radiotherapy regimen received: 66 to 74 Gy, standard fractionation Primary/adjuvant/other: Primary Other treatment received: NR
Interventions	Comparison: beclomethasone dipropionate vs placebo Arm 1: Daily 3 mg BDP enema during RT, and, subsequently, 2 x 3 mg BDP suppositories for 4 more weeks Arm 2: Daily placebo enema during RT, and, subsequently, 2 placebo suppositories for 4 more weeks
Outcomes	GI toxicity: Late RTOG/EORTC QoL: Modified IBDQ Other review outcomes: NR Other study outcomes: Valuation of the impact of topical BDP on patient's quality of life and the evaluation of risk factors associated with the development of radiation-induced proctopathy Duration of follow-up: 12 months
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...central randomisation."
Allocation concealment (selection bias)	Low risk	"Concealment of allocation sequence was guaranteed by the central randomisation."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Concealment of allocation sequence was guaranteed by the central randomisation. Double-blind method was used to ensure blinding of treatment assignment." Use of placebo
Blinding of outcome assessment	Low risk	"Double-blind method"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Low risk	Expected outcomes reported

Fuccio 2011 (*Continued*)

Other bias	Low risk	None noted
Overall judgement	Low risk	Based on the above

Gandhi 2013

Methods	Design: open parallel-arm RCT Country: India Trial Reg.: NR Accrual dates: Jan 2010 to Jan 2012 Funding source: NR
Participants	No. randomised:44 Inclusion criteria: Women with FIGO stage IIB - IIIB squamous cell cervical cancer; 25 to 65 years old; Karofsky performance status ≥ 70; normal range haematological, renal and liver function parameters Exclusion criteria: Women with non-squamous histology, para-aortic lymph nodes, metastases, or other malignancy Gender: Female Mean age: Intervention 50, Control 45 Type of cancer: Cervix Primary RT/adjuvant RT/other: Primary Other treatment received: All participants received concurrent weekly platinum-based chemotherapy (cisplatin 40mg/m^2) and HDR intracavitory radiation therapy ICRT (21Gy in 3 once-weekly fractions) or interstitial BT 10 Gy in 2 fractions after EBRT. All participants had CT-based planning in supine position and were immobilised with custom thermoplastic immobilisation devices
Interventions	Comparison: IMRT vs conRT Arm 1:IMRT: 50.4 Gy in 28 fractions over 5½ weeks; PTV D95 > 95%; constraints for normal tissue included small bowel V40 < 32%, maximum dose < 50 Gy; rectum V40 < 40%, maximum dose < 50 Gy; bladder V40 < 40%. Bone marrow was contoured but no dose constraint was given. The volume of small bowel receiving 90% and 100% of the the presciption doses was noted Arm 2: ConRT: 50.4 Gy in 28 fractions over 5½ weeks; 4-field box technique without blocks or shielding Bowel prep 92 tabs of bisacodyl in the afternoon and 2 tablets at night, 1 day before the planning CTs. Bladder-filling protocol (after voiding patients were asked to drink 1 litre of water 30 to 45 minutes before treatment and to hold urine)
Outcomes	GI toxicity: Acute and late (scale NR) QoL: NR Other review outcomes: Bowel dose volume Other study outcomes: Dosimetric parameters, DFS Duration of follow-up: Not stated in methodology but median follow-up was reported as 21.7 months (range 10.7 to 37.4) for the ConRT arm and 21.6 months (range 7.7 to 34.4) in the IMRT arm

Gandhi 2013 (*Continued*)

Notes	Baseline characteristics including stage of disease were comparable. At the last follow-up, 2 participants in the conRT and 1 in the IMRT arm had experienced local failure; 1 participant in the conRT arm and 3 in the IMRT arm had distant failures; and 1 participant in each arm had experienced simultaneous local and distant failure

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomised by random computer generation"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	"unblinded"
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No apparent missing data
Selective reporting (reporting bias)	Low risk	Expected outcomes reported but protocol not seen
Other bias	High risk	"Sample size was limited to 44 on the basis of resources" - underpowered, positive findings could have influenced the decision to stop at this point
Overall judgement	High risk	For reason stated above

Garcia-Peris 2016

Methods	Design: Randomised, double-blind, placebo-controlled trial Country: Spain Accrual dates: June 2005 to December 2007 Trial Reg.: NR Funding source: This work was supported in part by grants from Vegenat (Spain)
Participants	No. randomised: 48 Inclusion criteria: Female, age ≥ 18 years, and a diagnosis of gynaecologic cancer requiring postoperative pelvic RT Exclusion criteria: Previous RT, previous or adjuvant chemotherapy, other types of pelvic tumours or other gynaecologic malignancies, antibiotic or inmunosuppressive treatment 1 week before inclusion or during treatment, and the presence of acute or chronic gastrointestinal disease contraindicating ingestion of the fibre

	Gender: Female Age: Intervention: 60.2 (median), Control 60.4 (median) Type of cancer: Gynaecological Radiotherapy regimen received: 52.2 Gy in standard fractionation followed 1 week later by brachytherapy or 56 Gy in standard fractionation Primary/adjuvant/other: Primary Other treatment received: Written recommendations including exclusion of fibre and lactose were given to all participants to homogenise their diet. Participants were not permitted to eat foods produced by fermentation during treatment. The use of other prebiotics and probiotics were excluded. Concomitant pharmacotherapy with antimotility drugs, immunosuppressors, or antibiotics was not permitted. The need for any of these treatments led to the woman being withdrawn from the study
Interventions	Comparison: Prebiotic + diet restriction vs placebo + diet restriction Arm 1: The first group received 6 g twice daily for a mixture of fibre (50% inulin and 50% FOS) (Raftilose® Synergy 1 Orafti, Tienen, Belgium) dissolved in 200 ml water, from 1 week before to 3 weeks after RT. They also modified their diet (quantities not specified) to reduce fat, fibre and lactose Arm 2: The control group received 6 g of matching placebo (maltodextrin),dissolved in 200 ml water, twice daily from 1 week before to 3 weeks after RT. They also modified their diet (quantities not specified) to reduce fat, fibre and lactose
Outcomes	GI toxicity: NR CTC NCI QoL: EORTC-QLQ-C30 Global Health / Quality of Life Other review outcomes: NR Other study outcomes: NR Duration of follow-up: 3 weeks post-radiotherapy
Notes	The 2012 paper describes 40 participants enrolled and 31 analysed for changes in micrbiota and inflammatory markers (feacal calprotectin and DNA). No clinical (toxicity) end points are employed in this study. The focus of this paper was to see the effect of a mixture of inulin and fructo-oligosaccharide on lactobacillus and bifidobacterium (intestinal microbiota) of patients receiving radiotherapy. The 2016 article describes 48 participants enrolled and 38 analysed. This paper is entitled: *Effect of inulin and fructo-oligosaccharide on the prevention of acute radiation enteritis in patients with gynecological cancer and impact on quality-of-life*. Recruitment for both studies took place between June 2005 and December 2007. We took the results from the 2016 article, since this was the only article to contain clinical (toxicity) end points

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Low risk	Matching treatment sachets were placed in a coded box with sufficient sachets to last throughout the intervention period. The

Garcia-Peris 2016 (*Continued*)

		allocation was not known to investigators dispensing these coded boxes to participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and trial personnel including principal investigator blinded to allocation
Blinding of outcome assessment	Low risk	Allocation revealed only on completion of statistical analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	18% (8/46) dropout at end of RT. Groups balanced at baseline for age and tumour site
Selective reporting (reporting bias)	High risk	Most intended outcomes are reported but the authors are not explicit about the primary end point. The sample size required to demonstrate a difference of 10% between groups in incidence of grade 2 diarrhoea was 54. Grade 2 diarrhoea was defined as 4 of more bowel movements a day or night. No participants appeared to exhibit this frequency and thus all other end points (e.g. days with watery stool) were secondary and not powered
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	High risk	High risk overall due to risk of selective reporting

Gaya 2013

Methods	Design: RCT Country: UK Accrual dates: NR Trial Reg.: NR Funding source: NR. Prototype belly board was provided by Oncology Systems Limited
Participants	No. randomised: 30 (interim analysis). Target sample size is 50 Inclusion criteria: Biopsy-confirmed rectal adeno-carcinoma where the disease was considered at high risk of local recurrence by MRI staging, > 18 years old, ECOG performance status 0 - 2, informed consent. Participants had to be able to fit through the bore of the departmental scanner on the belly board and be independently mobile to get into either treatment position Exclusion criteria: Distant metastases, prior pelvic RT or neo-adjuvant chemo, contraindication to 5FU Gender: NR

Gaya 2013 (*Continued*)

	Age: Median 64 years Type of cancer: Rectal Radiotherapy regimen received: Radiotherapy as part of neoadjuvant chemoradiation: 45 Gy in 25 fractions over 5 weeks Primary/adjuvant/other: Other (neoadjuvant) Other treatment received: 5FU chemotherapy on weeks 1 and 5 as a radiosensitiser
Interventions	Comparison: Belly board versus no belly board Arm 1: Prototype belly board made of hollow core carbon fibre Arm 2: Standard protocol
Outcomes	GI Toxicity: Acute (CTCAE v3) (timing not stated) QoL: NR Other review outcomes: Reported participant comfort satisfaction on an adapted validated linear analogue scale Other study outcomes: Reproducibility of participant positioning and small bowel volume within radiation field; ease of set up Duration of follow-up: NR; acute toxicity assessed weekly
Notes	Patient comfort satisfaction scores were reported to be statistically significantly different between the groups in favour of the belly-board arm but we could not extract these data in a meaningful way for review purposes. No usable toxicity data: "No grade 4 toxicity was reported. In the belly board arm three patients developed the following grade 3 toxicities: proctitis, skin reaction, diarrhoea and pelvic pain. In the control arm, grade 3 toxicities reported in two patients included pelvic pain and skin reaction." Several dosimetric parameters were reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"random number table was used"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 participants did not complete their prescribed treatment and were excluded from the control arm post-randomisation
Selective reporting (reporting bias)	High risk	Interim analysis only. Acute toxicity reporting scant with events less than grade 3 not reported. No usable data

Other bias	Unclear risk	17 in belly-board arm and 13 in control arm - 2 participants in control arm were excluded from analyses (1 sustained a fractured femur unrelated to treatment and the other declined participation)
Overall judgement	High risk	Small sample with no usable data for meta-analysis in the interim report

Giralt 2008

Methods	Design: Placebo-controlled, double-blind, randomised clinical trial in 2 parallel groups Country: Spain Accrual dates: November 2002 to December 2005 Trial Reg.: NR Funding source: Supported by a grant from the Nutrition Department of Danone, Spain
Participants	No. randomised: 118 Inclusion criteria: Female gender, age > 18 years, a good performance status (ECOG functional status < 2), and a diagnosis of endometrial adenocarcinoma requiring post-operative pelvic RT or advanced cervical squamous cell carcinoma treated with pelvic RT and concomitant weekly cisplatin Exclusion criteria: Other types of pelvic tumours, such as gastrointestinal, urinary, or other gynaecologic malignancies, treatment with chemotherapy agents other than cisplatin, previous chemotherapy or RT, antimicrobial or immunosuppressors treatment at inclusion, and the presence of any acute or chronic gastrointestinal condition associated with diarrhoea in the month before recruitment Gender: Female Age: Intervention: 60.91 (mean) 11.8 SD, Control: 59.34 (mean) 12.77 SD Type of cancer: Cervical carcinoma, endometrial adenocarcinoma Radiotherapy regimen received: 45 Gy - 50.4 Gy in standard fractionation Primary/adjuvant/other: Primary and adjuvant Other treatment received: Women with cervical cancer received a weekly intravenous dose of cisplatin of 40 mg/m^2 during external beam RT
Interventions	Comparison: Probiotic vs placebo Arm 1: 96 mL 3 times daily of a fermented liquid yogurt containing approximately 10 (8) CFU/g of L. casei DN-114 001, in addition to the standard starters Streptococcus thermophilus and Lactobacillus delbrueckii, subsp. bulgaricus Arm 2: Same amount of matching placebo, prepared by sterilising the active product with 4 kGy administered for 5 mins
Outcomes	GI toxicity: Acute CTCAE v2.0 QoL: EORTC QLQ-C30 Other review outcomes: NR Other study outcomes: The secondary end points were the time to the development of Grade 2 diarrhoea, the interval to the first occurrence of Type 5, 6, or 7 stools, as

	determined from the Bristol scale, quality-of-life score, and safety Duration of follow-up: 6 months
Notes	Groups balanced at baseline for age, weight, QoL (QLQ-C30), tumour site, ECOG PS, RT v RTCT and diarrhoea grade

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation in blocks, stratified by tumour site
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial described as double-blind so participants and investigators blinded. Participants saw the same investigator at each assessment
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	The accrual goal (powered) was 154 participants. However, only 118 were randomised and of these, 33 were subsequently excluded due to ineligibility. Thus instead of the planned 77 per group, there were only 44 in the Intervention Group and 41 receiving the placebo, in total only 55% of those required
Selective reporting (reporting bias)	Low risk	All stated outcomes reported
Other bias	Low risk	Groups balanced at baseline for age, weight, QoL (QLQ-C30), tumour site, ECOG PS, RT v RTCT and diarrhoea grade
Overall judgement	Unclear risk	Unclear risk of bias due to the fact that IMRT now more commonly used than EBRT/conformal techniques. Study now nearly 10 years old

Gudipudi 2014

Methods	Design: Open parallel-arm RCT Country: India Trial Reg.: NR Accrual dates: Aug 2009 to Feb 2010 Funding source: NR
Participants	No. randomised: 50 Inclusion criteria: Women with FIGO stage IIA to IIIB cervical cancer; 20 - 85 years old Exclusion criteria: NR Gender: Female Type of cancer: Cervix Primary RT/adjuvant RT/other: NR Other treatment received: All women received concurrent weekly platinum-based chemotherapy (cisplatin 30 - 40 mg/m^2) and VBT
Interventions	Comparison: IMRT vs ConRT (ratio1:2) Arm 1: IMRT: 50 Gy in 25 fractions followed by VBT of 21 Gy in 3 Gy fractions Arm 2: ConRT: 50 Gy in 25 fractions followed by VBT of 21 Gy in 3 Gy fractions
Outcomes	GI toxicity: CTCAE v4 QoL: EORTC QLQ-C30 Other review outcomes: NR Other study outcomes: Response, recurrence and other toxicity Duration of follow-up: Unclear but selected outcomes were reported for 2, 5, 18 and 24 months
Notes	Conference abstract only. We could extract little/no methodological info or usable data from this report. "QoL was better in the IMRT group (P<0.01) based on functional, symptom, single-item and global scales,...". "Diarrhoea and financial problems were worse in the (conRT) group (P<0.05)." At 5 months, 30/35 and 14/15 had no locoregional recurrence, respectively. One woman in the IMRT arm died from a distant metastasis. At 18 months, 25/35 and 14/15 had no locoregional recurrence or distant metastases, respectively, and at 24 months 25/35 and 14/15 had no locoregional recurrence or distant metastases

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement

Gudipudi 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Gupta 2009

Methods	Design: RCT Country: India Accrual dates: Sept 2007 to August 2008 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 100 (83 analysed) Inclusion criteria: Histopathologically-proven, locally-advanced cervical cancer; informed written consent Exclusion criteria: NR Gender: Female Age: mean 51 and 48 years for the intervention and control groups, respectively Type of cancer: Cervix Radiotherapy regimen: 40 Gy to whole pelvis then 10 Gy with midline shield with EBRT at 2 Gy per fraction. Position of the participant was supine with hands over head. EBRT was followed by intracavitatory treatment Primary/adjuvant/other: Primary Other treatment received: NR
Interventions	Comparison: 4-field vs 2-field technique Arm 1: 4-field technique to include anterior, posterior and 2 lateral fields Arm 2: 2-field technique to include anterior and posterior fields
Outcomes	GI toxicity: Acute and late (RTOG) QoL: NR Other review outcomes: NR Other study outcomes: Local response and other toxicity Duration of follow-up: Weekly follow-up during treatment, then monthly for 1 year after completion of treatment. Outcomes were reported at end of RT, at week 6 and at month 6
Notes	Baseline characteristics including age, tumour stage, grade, treatment time, BT, and overall treatment time were comparable between the treatment groups. No difference was found between the arms in response to treatment
Risk of bias	

Gupta 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement: Authors reported that "patients were randomized either to four field box technique or two field technique" and "stratification factors were age, stage and Karnofsky performance status"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17% attrition. Toxicity data were only reported for participants that completed treatment (83) and the reasons for discontinuation of treatment were not reported. Authors stated "...patients who defaulted during treatment or whose treatment was not complete at the time of study were not included in the study"
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Habl 2016

Methods	Design: Open-label Phase II RCT Country: Germany Accrual: May 2012 to December 2013 Trial Reg.: NCT01641185 Funding source: Deutsche ForschungsgemeinschaftKlinische Forschergruppe Schwerionentherapie. Radioonkologie grant KFO 214
Participants	No. randomised: 92 (91 analysed) Inclusion criteria: Histologically-proven localised prostate cancer with risk of lymph node involvement < 15%, aged between 40 and 80 Exclusion criteria: Stage IV (distant metastases), lymphogenous metastases, hip replacement, former irradiation of the pelvis, pacemaker Gender: Male Age: Mean 68 years (rang 50 to 80)

Habl 2016 (*Continued*)

	Type of cancer: Prostate Radiotherapy regimen received: 66 Gy RBE administered in 20 fractions (single dose of 3.3 Gy RBE) Radiation was applied in 20 fractions, alternating between 5 and 6 fractions a week within a total of 3½ weeks Primary/adjuvant/other: Primary Other treatment received: 21 participants received antihormone treatment in addition to RT in a neoadjuvant/adjuvant setting. An absorbable gel (SpaceOAR; Augmenix, Waltham, MA) was injected between the rectum and the prostate 1 to 2 weeks before irradiation
Interventions	Comparison: Radiation with protons versus carbon ions Arm 1: Proton therapy Arm 2: Carbon ion therapy
Outcomes	GI toxicity: acute (CTCAE v3) QoL: EORTC QLQ C30 and PR25 Other review outcomes: Treatment discontinuation Other study outcomes: other toxicities, PSA-PFS, OS Duration of follow-up: NR. Follow-up at end of RT, at week 6 and month 6
Notes	Baseline characteristics were comparable between study arms including age, hormone therapy, initial PSA, Gleason score, tumour stage, D'Amico score, and Yale risk of lyph node involvement Two participants treated with proton therapy developed grade 3 rectal fistulas. Investigators therefore stopped using the spacer gel Reduced QoL was evident mainly in fatigue, pain, and urinary symptoms during therapy and 6 weeks thereafter. Authors concluded that hypofractionation with "either carbon ions or protons results in comparable acute toxicities and QoL parameters."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details to make a judgement, Described as "randomized phase III study"
Allocation concealment (selection bias)	Unclear risk	Insufficient details to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment	Unclear risk	Insufficient details to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout was recorded due to a small intestine loop directly next to the prostate
Selective reporting (reporting bias)	Unclear risk	Most expected outcomes reported, except late toxicity

Habl 2016 (*Continued*)

Other bias	Low risk	None noted
Overall judgement	Unclear risk	Insufficient details to make a judgement

Hejazi 2013

Methods	Design: Pilot Clinical Trial Country: Iran Accrual dates: March 2011 to March 2013 Trial Reg.: NR Funding source: Research grants from National Nutrition and Food Technology Research Institute, Iran National Science Foundation, and research deputy of Shahid Beheshti University of Medical Sciences. Arjuna Natural Extracts Ltd provided the tablets
Participants	No. randomised: 45 Inclusion criteria: Patients referred to local curative RT with EBRT, in combination with hormone ablation, adenocarcinoma of the prostate must be histologically confirmed on biopsy. All participants had a life expectancy > 5 years. No metastatic disease must be detected during physical examination, standard radiography, bone scan, and MRS. Additional inclusion criteria were no prior hormone therapy, radiotherapy or systemic treatment for prostate cancer and no other malignancy Exclusion criteria: Clinical stage T3 or T4, Gleason score ≥ 8, serum PSA ≥ 20 ng/mL, other prior surgery for prostate cancer, concurrent participation in another clinical trial which would require approval upon entry to this trial, gastrointestinal disorders such as inflammatory bowel disease, reflux and peptic ulcers and any adverse reaction to curcumin Gender: Male Age: Intervention: 69.58, Control 71.85 Type of cancer: Prostate Radiotherapy regimen received: 74 Gy in standard fractionation Primary RT/adjuvant RT/other: Primary Other treatment received: NR
Interventions	Comparison: Curcumin vs placebo Arm 1: Patients took 3 grams of curcumin (as 6 × 500 mg capsules, 2 capsules with each meal) 1 week before onset of RT until completion of their RT. Each curcumin capsule contained 440 mg curcuminoids (347 mg curcumin, 84 mg desmethoxycurcumin, and 9 mg bisdesmethoxycurcumin) and essential oil of turmeric 38 mg All participants were advised to avoid any changes in their usual dietary habits during intervention period Arm 2: Placebo (contained 500 mg roasted rice flour)
Outcomes	GI Toxicity: Acute, Persian version of the QLQ-PR25 QoL: Persian version of the QLQ-PR25 Other review outcomes: NR Other study outcomes: FFQ to assess polyphenol dietary intake Duration of follow-up: During RT and up to 3 months post-RT

Hejazi 2013 (*Continued*)

Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation lists using blocks of size 4
Allocation concealment (selection bias)	Unclear risk	Authors report that randomisation was done by administrative personnel outside the research project
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study with participants and researchers blinded to intervention
Blinding of outcome assessment	Low risk	Double-blind study with participants and researchers blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/22 withdrew from the Intervention group and 3/23 withdrew from the Placebo group. Authors report 40/45 participants complied with the intervention. Face-to-face meetings were conducted for questionnaire completion with no missing answers
Selective reporting (reporting bias)	High risk	Primary outcome and difference sought between groups not stated
Other bias	Unclear risk	Nutritional end points including total energy intake and polyphenol intake only reported at baseline but would have been more informative if reported post-RT as potential confounders
Overall judgement	High risk	Study may have been underpowered to detect a difference. Small study described as a pilot

Henriksson 1990

Methods	Design: Open randomised study Country: Sweden Accrual dates: NR Trial Reg.: NR Funding source: Part supported by grants from the Swedish Society Against Cancer and the Lion's Cancer Research Foundation, Umea, Sweden
Participants	No. randomised: 51 (45 analysed) Inclusion criteria: Women with gynaecological malignancies. Exclusion criteria: NR Gender: Female Age: NR Type of cancer: Gynaecological (10 ovarian, 17 endometrial, 18 cervical) Radiotherapy regimen received: Dose NR? cervical and endometrial stage I and II received intracavity treatment. External RTwas given with 6 and 20.9 MV photons, Dose planning was made individually. Whole pelvis irradiation was given to participants with ovarian carcinoma and in more advanced stages of cervical carcinoma Primary/adjuvant/other: Primary and adjuvant Other treatment received: NR
Interventions	Comparison: Sucralphate vs control Arm 1: Sucralfate (andapsin) was dispensed to each participant when RT started. Participants instructed to ingest 2 g 4 times daily Arm 2: RT alone
Outcomes	GI toxicity: Acute Unvalidated Scale QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used
Blinding of outcome assessment	Low risk	"The evaluation of the result was undertaken by an independent person (R.H.) without knowing whether the patient received sucralfate or not"

Henriksson 1990 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	51 randomised - 6 excluded early (4 in sucralfate group and 2 in control group); 2 in the sucralfate group probably withdrew due to side effects
Selective reporting (reporting bias)	High risk	Authors conclude that there was less diarrhoea in the sucralfate group than the control group, but according to Table 3, the opposite is true. These data are inconsistent with Table 4
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Henriksson 1991

Methods	Design: Double-blind, placebo controlled Country: Sweden Accrual dates: March 1988 to June 1989 Trial Reg.: NR Funding source: Part supported by grants from the Swedish Society Against Cancer and the Lion's Cancer Research Foundation, Umea, Sweden. Kristina Puzey and Farmos Group AB, Stockholm, for supply of drugs and support during the study
Participants	No. randomised: 70 Inclusion criteria: Patients with primary diagnosis of carcinoma of the prostate or urinary bladder with performance status of 90% or greater Karnofsky scale Exclusion criteria: Patients with pre-exisitng gastrointestinal problems who had undergone intestinal surgery, colostomy and previous chemotherapy or RT Gender: NR Age: NR Type of cancer: Carcinoma of prostate and urinary bladder Radiotherapy regimen received: 62 Gy to 66 Gy with 1.8 - 2.2 Gy daily fractions Primary/adjuvant/other: Primary Other treatment received: NR
Interventions	Comparison: Sucralfate vs placebo Arm 1: Dose granules of sucralfate dispensed 2 weeks after RT started, with instuctions to ingest 1 dose package(1 g) dissolved in water 6 times daily for 6 weeks Arm 2: Placebo identical in taste, colour and consistency
Outcomes	GI toxicity: Acute Unvalidated Scale QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT until 1 year after RT

Henriksson 1991 (*Continued*)

Notes	56 participants were assessable for follow-up 12 to 14 months after termination of the RT. 8 participants died because of tumour progression,and 2 refused further evaluation and did not wish to leave their local hospital. These 2 participants needed operations for other diseases

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Low risk	"The statistical analysis and evaluations were performed blindly by an independent statistician..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants in the sucralfate group were excluded early (1 disagreed with the study design, 1 had vertigo that required treatment elsewhere, and 1 had a new malignancy) and 1 participant in the control group withdrew due to constipation
Selective reporting (reporting bias)	Low risk	Protocol not seen but expected outcomes were reported
Other bias	Low risk	None noted
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Hille 2005

Methods	Design: Phase III randomised, placebo-controlled, double-blind trial Country: Germany Accrual dates: May 2003 to April 2004 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 100 Inclusion criteria: All patients with prostate carcinoma who were treated with RT to achieve local control were eligible for the study Exclusion criteria: Stage T4 carcinoa, bowel movements > 5 daily, a history of inflam-

	matory bowel disease, and expected non-compliance Gender: Male Age: Intervention: 68.3 (mean), Control: 67.8 (mean) Type of cancer: Prostate Radiotherapy regimen received: 45 Gy - 72 Gy in standard fractionation and boost Primary/adjuvant/other: Primary Other treatment received: NR
Interventions	Comparison: Misoprostol vs placebo Arm 1: Rectal suppositories with misoprostol 1 hour before each RT session. The rectal suppositories were prepare with 2 200 ug tablets of Cytotec (Parmacia?heumann, Nurnberg) Arm 2: Identical-looking placebo (suppositories prepared with fat)
Outcomes	GI toxicity: Acute CTC, RTOG/LENT-SOMA QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: Median 50 months
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind randomisation; placebo looked indentical
Blinding of outcome assessment	Low risk	Double-blind randomisation; placebo looked identical, "The pharmacist of the University of Goettingen produced the suppositories and performed the randomization for this study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Low risk	Baseline characteristics were distributed similarliy in both treatment arms

Hille 2005 (*Continued*)

Overall judgement	Unclear risk	Insufficient detail to make a judgement

Hombrink 2000

Methods	Design: Randomised double-blind trial Country: Germany Accrual dates: April 1994 to May 1995 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 176 Inclusion criteria: Pelvic irradiation, irradiation of the entire abdominal or abdominal fields in the sense of an "inverted ypsilon" Exclusion criteria: Patients with concomitant morphine therapy, any other co-therapy with motility inhibitors, astringents and adsorbents, antacids, antibiotics and enteric-acting micro-organisms, chemotherapy within the last 2 weeks before irradiation, combined radiochemotherapy, patients with chronic constipation, pregnancy, lactation and fertile women without contraception Gender: 33% male Age: NR Type of cancer: Cervix, corpus uteri, rectal, prostate, lymphatic, others Radiotherapy regimen received: Linear accelerators with energies between 9 and 16 MeV photons. In 74 participants (Colina® group 34, placebo group 40), additional afterloading therapy was performed in addition to percutaneous RT using fractionation and single or total dose Primary/adjuvant/other: Primary and adjuvant Other treatment received: Surgery. 65% had tumours removed
Interventions	Comparison: Smectite vs placebo Arm 1: The Colina® group received 6 g of smectite twice a day (2 times 2 bags each with 3 g, daily total dose = 12 g) This was taken approximately 1 hour before or during a meal. The application began simultaneously with irradiation and was continued throughout the irradiation period Arm 2: The placebo group received corresponding bags with a mixture of starch, maltodextrin, glucose hydrate and Na-saccharin. This was taken approximately 1 hour before or during a meal. The application began simultaneously with irradiation and was continued throughout the irradiation period
Outcomes	GI toxicity: Unvalidated investigators' scale QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: NR
Notes	This study assessed GI toxicity of RT-induced diarrhoea against prophilactic effect of smectite (Colina). The end point of the analysis was the first occurrence of diarrhoea (defined as ≥ 3 unformed stools per day). The median time to first occurrence of diarrhoea was 20 days (95% CI 17 to 32 days) in the Colina® group, or 18 days (95% CI 15 to

	26 days) in the placebo group. In an exploratory post hoc analysis the total study group was split up into 2 subgroups, 1 with an irradiated small bowel volume ≤ 837.5 ml, the other with a small bowel volume > 837.5 ml (median); the analysis indicated that the first subgroup showed a benefit for the smectite-treated participants in contrast to the placebo treatment (32 vs 18 calendar days to the first appearance of diarrhoea). This benefit was .statistically not significant'

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Low risk	The group was assigned before the first irradiation day with the aid of prepared, closed and randomised study medication
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Similar-looking placebo was used
Blinding of outcome assessment	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	29 participants (Colina group 15, placebo group 14) terminated prematurely or were excluded from the per protocol analysis. 77 side effects in total were observed, leading to 8 participants (5 Colina Group, 3 placebo group) terminating study prematurely. However, ITT and per protocol analyses are reported
Selective reporting (reporting bias)	Unclear risk	Outcome measures were not those commonly measured and few data could be extracted
Other bias	Low risk	None noted
Overall judgement	Unclear risk	Limited reporting of study methods

Hovdenak 2005

Methods	Design: Prospective, randomised, placebo-controlled study Country: Norway Accrual dates: December 1999 to June 2000 Trial Reg.: NR Funding source: The drug (AntepsinÒ) and the placebo tablets, supplied by Orion Pharma A/S, Oslo, Norway
Participants	No. randomised: 52 Inclusion criteria: Consecutive patients with localised pelvic tumour, scheduled for curative external pelvic RT Exclusion criteria: Significant current or previous gastrointestinal disease (ulcerative colitis, Crohn's disease, coeliac disease) were excluded. Patients with irritable bowel syndrome were allowed to participate, but none fulfilled the Rome II criteria for this diagnosis Gender: NR Age: NR Type of cancer: Localised pelvic tumour Radiotherapy regimen received: 64 - 70 Gy standard fractionation Primary/adjuvant/other: Primary Other treatment received: NR
Interventions	Comparison: sucralfate vs placebo Arm 1: Peroral sucralfate 2 g 3 times daily was given during the course of RT, starting on first day of RT Arm 2: Identical-appearing placebo tablets
Outcomes	GI toxicity: Acute Unvalidated Scale QoL: NR Other review outcomes: NR Other study outcomes: Secondary end points include changes in other gastrointestinal symptoms, endoscopic findings, and histological parameters. Authors reported that at 2 and 6 weeks into treatment "Mean diarrhoea score was significantly higher (P = 0.049 and P = 0.033, respectively) among patients treated with sucralfate than in the placebo group. An intention to treat analysis showed a statistically significant difference in favour of placebo at week 6 (P=0.007)." Data on abdominal pain, tenesmus and bloating were presented graphically and could not be imputed. However, no statistically significant differences were noted for these outcomes Duration of follow-up: Study was halted early.
Notes	On the basis of previously published negative reports, an unplanned interim analysis of 44 evaluable participants showed significantly increased diarrhoea in the sucralfate group and the trial was stopped

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement

Hovdenak 2005 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled, randomised, double-blind, identical-appearing placebo tablets
Blinding of outcome assessment	Low risk	Placebo-controlled, randomised, double-blind, identical-appearing placebo tablets
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4/24 and 3/27 participants were excluded from the analysis due to protocol violations
Selective reporting (reporting bias)	High risk	On the basis of previously published negative reports, an unplanned interim analysis of 44 evaluable participants showed significantly increased diarrhoea in the sucralfate group and the trial was stopped
Other bias	High risk	On the basis of previously published negative reports, an unplanned interim analysis of 44 evaluable participants showed significantly increased diarrhoea in the sucralfate group and the trial was stopped
Overall judgement	High risk	Based on limitations above

Huddart 2013

Methods	Design: Non-blinded, multicentre, non-inferiority RCT in 28 UK hospitals Country: UK Accrual dates: Aug 2001 to April 2008 Trial Reg.: ISRCTN68324339 Funding source: Cancer Research UK
Participants	No. randomised: 219 Inclusion criteria: T2 - T4aN0M0 bladder cancer (adenocarcinoma or transitional or squamous cell carcinoma); WHO performance status grade 0 - 2, leucocytes > 4.0 109/L, platelets > 100 109/L, Glomerular filtration rate (GFR) > 25 mL/min, and serum bilirubin, ALT, or AST < 1.5 upper limit of normal. Platinum-based neoadjuvant chemotherapy was permitted but not mandatory. Written informed consent. Participation in an additional randomisation to synchronous chemotherapy was optional Exclusion criteria: Other malignancy in the past 2 years, previous pelvic RT, bilateral hip replacements, pregnancy, inflammatory bowel disease Gender: 82% male Type of cancer: Bladder cancer Radiotherapy regimen received: Centres opted at study outset to use either 55 Gy/20 fractions over 4 weeks or 64 Gy/32 fractions over 6½ weeks for all participants. 3DCRT

	was used Primary/adjuvant/other: Mostly adjuvant (90% had tumour resection) Other treatment received: A double randomisation to synchronous chemotherapy was optional. In additional neoadjuvant chemotherapy was planned for some participants (and randomisation was stratified accordingly)
Interventions	Comparison: Reduced dose volume versus standard dose volume Arm 1: Reduced high-dose volume RT (RDHVRT): 2 PTVs were defined: PTV1 as per sRT; and PTV2 as gross tumour plus a 1.5 cm margin. Aim was to deliver 100% of the reference dose to PTV2 and 80% of the reference dose to PTV1 using 3 or 4 coplanar fields Arm 2: standard RT (sRT): PTV was outer bladder wall plus the extravesical extent of the tumour with a margin of 1.5 cm. 4-field technique was used to encompass the PTV in the 95% isodose
Outcomes	GI toxicity: Acute and late (RTOG) QoL: NR Other review outcomes: NR Other study outcomes: LENT-SOMA scale used for 'Any toxicity', local recurrence, overall survival, bladder capacity Duration of follow-up: 2 years; assessed weekly during treatment, then at 6, 9 and 12 months, then annually
Notes	Baseline characteristics were comparable between groups, including age, tumour stage, grade, performance status, neoadjuvant chemotherapy,tumour size, residual tumour mass, RT regimen planned, dose received, and dose delays of 7 days or more. Toxicity was reported according to per protocol. On the LENT-SOMA scale (for any late toxicity during follow-up) there was no difference between the groups (P = 0.38)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer-generated random permuted blocks were used, stratified by treatment centre, planned neoadjuvant chemotherapy and…" entry to this and a second randomisation
Allocation concealment (selection bias)	Low risk	"...independent randomisation was via telephone to the Institute of Cancer Clinical trials and Statistics Unit"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"non-blinded"
Blinding of outcome assessment	Low risk	"Central statistical monitoring and all analyses were conducted at ICR-CTSU." (In-

Huddart 2013 (*Continued*)

		stitute of Cancer Research Clinical Trials and Statistics Unit, UK)
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 participants randomised were found to be ineligible. In total 22 participants were excluded from the per protocol analysis on toxicity including 13 randomized to RHD-VRT who received sRT
Selective reporting (reporting bias)	Low risk	Expected outcomes reported (protocol not seen). "Central data management was performed by ICR-CTSU". "The trial was overseen by an independent trial steering committee."
Other bias	Low risk	Baseline characteristics comparable between groups
Overall judgement	Low risk	Well-conducted trial

Itoh 2015

Methods	Design: Randomised, placebo-controlled, double-blind pilot trial Country: Japan Accrual dates: NR Trial Reg.: NR Funding source: Daiwa Pharmaceutical Co., Ltd., the manufacturer of both the HRB and placebo foods, which were provided free of charge
Participants	No. randomised: 20 Inclusion criteria: Patients with primary squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma located in the cervix were included. (i) age of $\geq$ 20 to < 75 years at the time of providing informed consent; (ii) cervical cancer with the intent for chemoradiotherapy; (iii) adequately-maintained major organ function (bone marrow, liver, and kidneys) and laboratory parameters within the following ranges: white blood cell count of > 3500/mm^3, absolute neutrophil count of > 1500/mm^3, haemoglobin A1c level of $\geq$ 10.0 g/dL, platelet count of $\geq$ 100,000/mm^3, total bilirubin level of $\leq$ 1.5 mg/dL, AST and ALT levels of < 80 IU/L, serum creatinine level of < 1.5 mg/dL, and creatinine clearance rate of $\geq$ 60mL/min (Cockcro -Gault formula or 24-hour creatinine clearance); and (iv) having received an explanation of the purpose and methods of this trial and having provided written consent prior to the start of the trial Exclusion criteria: Patients with small cell carcinoma or sarcoma were excluded. (i) undergoing surgical treatment; (ii) undergoing a nonsurgical treatment thought to affect treatment with HRB and its outcome; (iii) presence of a drug allergy; (iv) known or possible pregnancy, desire to become pregnant, or currently breastfeeding; and (v) other conditions that the principal investigator or a coresearcher thought might make an individual unsuitable for this study Gender: Female

	Age: Intervention: 47.5 (median) 30 - 72 (range), Control: 47.5 (median) 30 - 72 (range) Type of cancer: Cervical cancer: 18 squamous cell carcinoma and 2 adenosquamous carcinoma Radiotherapy regimen received: EBRT 50.4 Gy in standard fractionation and brachytheraphy Primary/adjuvant/other: Primary Other treatment received: Chemotherapy regimen was performed every 3 weeks: cisplatin at 70 mg/m^2 on day 1 and a continuous infusion of 5-FU at 700 mg/m^2 on days 1 to 4
Interventions	Comparison: hydrolysed rice bran (HRB) vs placebo Arm 1: 3 packets of the HRB (1 g of HRB per packet) were taken orally 3 times a day. The HRB was consumed before the start of chemoradiotherapy (up to 1 week before) and it was taken every day while receiving RT. Use of each drug has been also stopped simultaneously with EBRT end Arm 2: Identical-looking placebo. 3 packets of the placebo food were taken orally 3 times a day
Outcomes	GI toxicity: Acute CTCAE v 3.0 QoL: NR Other review outcomes: NR Other study outcomes: Secondary end points were the frequency and severity of gastrointestinal symptoms other than diarrhoea (nausea, vomiting, and loss of appetite) and NK cell activity Duration of follow-up: During RT
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Low risk, authors state that participants were blinded to treatment group
Blinding of outcome assessment	Low risk	Low risk, authors state that participants' doctors were blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Recruited 20 but only analysed 14 due to exclusions, mainly based on non-compliance due to chemo-induced nausea and vomiting

Itoh 2015 (*Continued*)

Selective reporting (reporting bias)	High risk	Prespecified outcomes have been reported but the methodology of deriving the final scores (i.e. diarrhoeal side effect assessment score) is not provided
Other bias	High risk	Small non-powered trial. Methodology for deriving primary end point unclear
Overall judgement	High risk	High risk overall

Jahraus 2005

Methods	Design: Double-blind RCT Country: USA Accrual dates: January 2003 to July 2004 Trial Reg.: NR Funding source: University funded. Drug and placebo were provided by Salix Pharmaceuticals. The second author of the study is an employee of Salix Pharmaceuticals
Participants	No. randomised: 27 Inclusion criteria: Pathologically-confirm diagnosis of prostate cancer, American Joint Committee on Cancer Stage T1 - 3, MO, or biochemical recurrence of prostate cancer after prostatectomy scheduled to receive regimen of external beam pelvic RT with a dose of at least 45 Gy in a 4-field technique and a minimum total tumour dose of 64 Gy, Karnofsky performance status > 70%, willing to complete protocol-specified evaluations according to schedule, willing and able to provide written informed consent for study participation, and age > 18 years Exclusion criteria: prior history of pelvic/abdominal irradiation, stool incontinence, stool frequency of > 6 per day, history of IBD, known salicylate hypersensitivity or current or prior use of any 5-ASA drug Gender: Male Age: Intervention: 67.7 (mean), Control: 67.5 (mean) Type of cancer: Urological (prostate) Radiotherapy regimen received: 45 Gy in standard fractionation Primary/adjuvant/other: Primary and adjuvant Other treatment received: NR
Interventions	Comparison: balsalazide vs placebo Arm 1: 2250 mg balsalazide twice daily beginning 5 days before RT and continuing 2 weeks after completion Arm 2: Identical-looking placebo
Outcomes	GI Toxicity: NCICTC v2.0 QoL: (scale used) NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT plus a 2 week post-treatment visit

Notes	None noted	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized by sealed envelope decision, with only the protocol coordinator aware of the results of randomization"
Allocation concealment (selection bias)	Unclear risk	"Patients were randomized by sealed envelope decision, with only the protocol coordinator aware of the results of randomization"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients were randomized by sealed envelope decision, with only the protocol coordinator aware of the results of randomization"
Blinding of outcome assessment	Low risk	"Physicians responsible for toxicity grading were blinded to the results of randomization." "placebo, identical in their appearance." "a randomized double-blind" trial. "In the event a patient developed a severe adverse event, deemed by the treating physician potentially related to the study drug, the patient's randomization status was unblinded to a physician not involved in toxicity scoring, and the most appropriate intervention was determined and implemented."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Methodology is poorly described

Kardamakis 1995

Methods	Design: Prospective, randomised, double-blind study Country: NR Accrual dates: October 1988 to April 1990 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 33 Inclusion criteria: Patients with histologically-confirmed tumours of prostate, urinary bladder, and cervix Exclusion criteria: NR Gender: NR Age: NR Type of cancer: Prostate (10), urinary bladder (13), cervix (10) Radiotherapy regimen received: Standard fractionation for at least 4 days a week for 5 to 6½ consecutive weeks Primary/adjuvant/other: Primary Other treatment received: NR
Interventions	Comparison: tropisentron vs control Arm 1: 6 weeks treatment with tropisetron (25 mg daily) starting same day as RT Arm 2: 3 weeks treatment with placebo followed by 3 weeks treatment with tropisetron (25 mg) starting same day as RT Arm 3: 6 weeks treatment with placebo starting same day as RT
Outcomes	GI toxicity: Acute Unvalidated QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: NR
Notes	9 participants withdrew from the study - all 33 participants were included in the evaluation of efficacy and tolerance

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement

Kardamakis 1995 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	High risk	Poorly reported study

Katsanos 2010

Methods	Design: Randomised phase II exploratory clinical trial Country: Greece Accrual dates: May 2001 - ? Trial Reg.: NR Funding source: NR
Participants	No. randomised: 44 Inclusion criteria: Primary pelvic or metastatic to the pelvis malignancies who were referred for adjuvant, radical or palliative radiotherapy but not for re- irradiation. Older than 18 years, had a WHO performance status 0 - 2 and a life expectancy of > 6 months Exclusion criteria: Pregnant or lactating women, patients with severe infections or severe psychiatric or neurologic illnesses. Patients with decreased haematologic reserves, with major organ failure, severe electrolyte or metabolic abnormalities. Patients with symptomatic hypotension , previous history of chronic colitis, non-specific proctitis, ulcerative colitis, diverticular disease or on treatment with non-steroidal anti-inflammatory drugs Gender: 52% male Age: Intervention: 59 (median), Control: 62 (median) Type of cancer: Rectal (20/44), cervical (12/44), prostate (5/44), urinary bladder (3/44) , endometrial (2/44), pelvic sarcomas (2/44) Radiotherapy regimen received: Mean total dose 50.4 Gy for study group and 50.2 Gy for control group normal fractionation Primary/adjuvant/other: Primary Other treatment received: In participants with haemoglobin levels below 11 g/dl before RT, subcutaneous erythropoietin was administered. Participants with hypertension controlled with medication were eligible for amifostine administration
Interventions	Comparison: Amifostine vs control Arm 1: Amifostine (subcutaneously, 500 mg flat dose) (5 days/week), 20 - 30 minutes before RT Arm 2: RT alone
Outcomes	GI toxicity: Acute and late CTC version 2.0 QoL: NR Other review outcomes: NR Other study outcomes: endoscopic findings Duration of follow-up: Prior to and post-RT, and again 6 to 9 mths later

Katsanos 2010 (*Continued*)

Notes	The was a gender imbalance between the groups CTCAE toxicity measured but not reported. We used the endoscopic findings in our meta-analysis (and considered these to be potentially high risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment	High risk	Unclear whether the endoscopist was blind to group allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	High risk	Despite reporting that CTCAE v 2 was used, these data were not reported. Only endoscopic findings were reported
Other bias	Low risk	None noted
Overall judgement	High risk	Due to methodological and reporting limitations

Kilic 2000

Methods	Design: Double-blinded, randomised, placebo-controlled Country: Turkey Accrual dates: August 1997 to April 1999 Trial Reg.: NR Funding source: NR
Participants	No. randomised:87 Inclusion criteria: Current histological proof of cancer in the pelvis and no distant metastases beyond the regional lymph nodes who were scheduled for external beam pelvic RT Exclusion criteria: Lack of a functioning rectum, stool incontinence, stool frequency > 6 bowel movements a day, if perineum was in the planned irradiation volume, digoxin use, history of prior pelvic/abdominal irradition, inflammatory bowel disease, known salicylate hypersensitivity, nephrotic syndrome, hepatic values of twice the normal or Karnofsky performance Status < 70. Patients could not participate in any protocol. No

	systemic administration of cytotoxic chemotherapy was allowed during RT Gender: 56% male Mean age: Intervention: 60 years, Control: 61 years Type of cancer: Rectum/rectosigmoid (42/87), endometrium (12/87), cervix uteri (8/87), prostate (14/87), bladder (10/87), pelvic sarcoma (1/87) Radiotherapy regimen received: 46 - 50 Gy in standard fractionation Primary/adjuvant/other: Primary Other treatment received: After completion of pelvic RT, tumour boost was allowed either with brachytherapy (for gynaecologic cancers), or external beam irradiation (prostate and bladder) according to tumour site
Interventions	Comparison: Sulfasalazine vs placebo Arm 1: 1000mg sulfasalazine twice daily for 5 weeks Arm 2: Identical-looking placebo tablets twice daily
Outcomes	GI Toxicity: Acute LENT-SOMA QoL: (scale used) NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: Until RT was completed, unless particioant began to experience 7 or more stools/day above the pretreatment baseline
Notes	2 papers (2001 and 2000) reported different sample sizes (31 and 87, respectively) accrued during an overlapping time period; we assumed these to be the same study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized by a different physician from the one treating before RT. Patients were randomized in a double-blind fashion"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients were randomized in a double-blind fashion"
Blinding of outcome assessment	Low risk	"All gradings were done in a blinded fashion"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"No losses to follow up, no refusals to continue the trial without any side effects, and no complications due to the drug."
Selective reporting (reporting bias)	Low risk	Expected outcomes reported

Kilic 2000 (*Continued*)

Other bias	Unclear risk	2 papers (2001 and 2000) reported different sample sizes (31 and 87, respectively) accrued during an overlapping time period; we assumed these to be the same study
Overall judgement	Unclear risk	Insufficient detail on randomisation method and the confusing reports with different sample sizes

Kim 2002

Methods	Design: RCT Country: USA Accrual dates: 1991 to 1997 Trial Reg.: NR Funding source: National Cancer Institute
Participants	No. randomised: 184 (152 analysed) Inclusion/exclusion criteria: receiving RT as curative treatment for localised prostate cancer as outpatients, no previous or concurrent cancer diagnosis (except basal cell skin cancer), able to speak and read English, no history of mental illness or alcoholism, capable of meeting daily basic needs independently (Karnofsky Performance status of at least 80%), and 18 years of age or older Gender: Male Mean age: Cohort (n = 152) was 70.8 yrs (range 44 - 85) Type of cancer: Prostate Radiotherapy regimen received: Primary
Interventions	Arm 1: Participants listened to brief tape-recorded messages in the clinic before their first and fifth RT sessions. The lengths of the audio-only tapes were 4 and 8 minutes, respectively, for these 2 treatments. The tapes were designed to deliver specific, descriptive, sensory messages regarding RT procedures and related information based on self-regulation theory, in addition to the same self-care instruction as was given to the comparison group. The information was developed from descriptive data collected from men undergoing RT for prostate cancer [10] and was tailored to match the standard practices of the RT facility of each participating institution.Clinic personnel then answered all questions participants had concerning their treatments Arm 2: The tape-recorded messages containing general and global information that was generally available to all RT patients, including resources available to them in the treatment setting. Clinic personnel answered all questions patients had concerning their treatments
Outcomes	GI toxicity: (acute) 5-point VAS, POMS QoL: on 5-point VAS, POMS Other review outcomes: NR Other study outcomes: NR Duration of follow-up: measured before and at last RT

Kim 2002 (*Continued*)

Notes	Baseline characteristics were not compared in the report	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described other than "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 184 enrolled, data from 32 (17%) were excluded due to protocol errors
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	Baseline data not compared in the report. 8 participating centres; recruitment numbers for each centre were not reported
Overall judgement	Unclear risk	Due to methodological limitations above

Kneebone 2001

Methods	Design: Multi-institutional, placebo-controlled, double-blind randomised study Country: Australia Accrual dates: February 1995 - June 1997 Trial Reg.: NR Funding source: Supported in part by a grant from Chugai Pharmaceuticals, as well as from the Radiation Oncology Trust Fund from the Prince of Wales Hospital
Participants	No. randomised: 338 Inclusion criteria: Patients planned to receive definitive irradiation for a clinically-localised prostate cancer. Dose had to be 60 Gy or more, and the superior limit of the treatmnet field was situated below the level of the greater sciatic notch, to ensure that significant portions of the small bowel were not irradiated Exclusion criteria: Active gastrointestinal conditions, including diverticulitis, Crohn's disease, ulcerative colitis, and colostomy formation. Patients with haemorrhoids were not excluded. Patients with significant renal impairment (serum creatinine > 30.3 mmol/L) were excluded Gender: Male

Kneebone 2001 (*Continued*)

	Age: Intervention: 67.6 (44 - 84), Control: 67.7 (47 - 84) mean (range) Type of cancer: Prostate Radiotherapy regimen received: 60 Gy to 72.2 Gy standard fractionation Primary/adjuvant/other: Primary Other treatment received: NR
Interventions	Comparison: Sucralfate vs placebo Arm 1: 15 mL (3 g) sucralfate (formulated as a suspension) twice a day, starting 1 day before irradiation and continuing every day for 8 weeks. The suspension was contained in a 500 mL bottle, with the Pharmacy collected at the end of each fortnight and replaced with a new one. Each participant received 4 bottles in total. If RT was delayed by more than 1 week, the trial medicine was withheld until the reinstitution of RT Arm 2: Identical-looking placebo
Outcomes	GI toxicity: Acute and late RTOG/EORTC QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: Every 3 months after RT completion for a total of 8 interviews within a 2-year period
Notes	Reported maximum and average pain scores per day, flatus per day, % of days with mucus and other non-review outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Confidential computer-generated list of patient trial numbers and treatment assignments"; "one-to-one stratified allocation in blocks of eight" per institution
Allocation concealment (selection bias)	Low risk	Via "phone call to central trial manager" once the participant was registered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients…were blinded to the allotted treatment"; "Investigators, data managers and pharmacy…were blinded to the allotted treatment
Blinding of outcome assessment	Low risk	"Investigators, data managers and pharmacy…were blinded to the allotted treatment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	298 evaluated (88%); reasons for attrition reported and balanced (9 in each group)

Kneebone 2001 (*Continued*)

Selective reporting (reporting bias)	Low risk	Protocol not seen but expected outcomes were reported
Other bias	Low risk	None noted
Overall judgement	Low risk	Based on above

Koper 1999

Methods	Design: Open-label parallel-arm RCT Country: The Netherlands Trial Reg.: NR Accrual dates: June 1994 to March 1996 Funding source: The "Revolving Fund" of the University Hospital Rotterdam
Participants	No. randomised: 266 Inclusion criteria: T1-4N0M0 prostate cancer without prior pelvic radiotherapy with any tumour stage, grade and PSA level Exclusion criteria: History of other malignancy Gender: Male Type of cancer: prostate Primary/adjuvant/other: Primary Other treatment received: No neoadjuvant hormone therapy used
Interventions	Comparison: 3DCRT vs conRT Arm 1: 3DCRT: Total dose of 66 Gy in 2 Gy fractions 5 times a week with conformally-shaped fields using a multileaf collimator Arm 2: ConRT: Total dose of 66 Gy in 2 Gy fractions 5 times a week with standard rectangular radiation field PTV was defined as the gross target volume + 15 mm
Outcomes	GI toxicity: Acute and late (EORTC-RTOG and patient-reported questionnaire with symptoms coded 1 to 4 with increasing severity (2004 paper only)). Overall scores were defined by the maximum score of any of the intestinal items of the questionnaire QoL: NR Other review outcomes: NR Other study outcomes: OS Duration of follow-up: Not clearly described but acute data are presented and follow-up is mentioned at 1 year and 2 years post-treatment in Koper 2004
Notes	25% of participants had GI symptoms at the start of treatment and this correlated with late GI symptoms scores on the patient self-assessment questionnaire. Individual symptoms reported included the percentage of participants reporting moderate/severe cramps (5%), faecal loss (55%), faecal mucus (4%), urgency (2%), soiling (5%), and blood (5%) - these were reported for the cohort as a whole at 2 years after treatment, and not by group

Koper 1999 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"patients were enrolled in a randomised study"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	"unblinded"
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Toxicity data were available for 248/266 participants randomised: 3 were excluded because of death, 7 because of loco-regional recurrence and 7 due to missing data or loss to follow-up. For 32 participants lacking 2-year data, the scores at 1 year follow-up were used
Selective reporting (reporting bias)	Low risk	Expected outcomes reported but protocol not seen
Other bias	Low risk	None noted
Overall judgement	Low risk	Good-quality RCT

Koukourakis 2000

Methods	Design: Randomised Phase II study Country: Greece Accrual dates: July 1997 to May 1999 Trial Reg.: NR Funding source: This study was designed, analyzed, interpreted and financially supported by the Tumour and Angiogenesis Research Group, Crete, Greece. Schering-Plough and U.S. Bioscience provided financial support
Participants	No. randomised: 140 Inclusion criteria: WHO performance status 2 or less and referred for radical postoperative RT because of locally-advanced inoperable cancer or residual mass or positive histologic margins after surgery but no evidence of distant metastases. Written consent obtained Exclusion criteria: Previous RT or chemo or WMC counts less than 2500/uL and platelet counts less than 100,00/uL, haemoglobin < 10 g/dL received transfusions until above 11g/dL. Pregnancy, major heart, lung, liver,, renal or neurologic/psychiatric disease,

	haematologic malignancies. Cardiac infarction that occurred 6 months of earlier were eligible. Hypertension controlled by medication eligible. Clinically-evident pulmonary insufficiency (exertional dyspnoea) were excluded. However, external dyspnoea related to chest tumour itself was eligible. Serum creatinine or liver enzyme serum higher than 1.5 and 2.5 times normal excluded Gender: 79.3% male Age mean (range): Intervention: 66 (34 - 78), Control: 63 (35 - 74) Type of cancer: Lung carcinoma (60/140), head and neck carcinoma (40/140), pelvic carcinoma (40/140) Radiotherapy regimen received: 44 to 70 Gy (depending on site) standard fractionation Primary/adjuvant/other: Primary and adjuvant Other treatment received: All participants pretreated with 5 mg oral tropisetron 1 to 2 hours before subcutaneous injection of amifostine Patients with haemoglobin < 10 g/dL received transfusions until above 11g/dL
Interventions	Comparison: Amifostine vs control Arm 1: Flat dose of amifostine 500 mg, diluted in 2.5 mL of normal saline, injected subcutaneously, repeated daily, 20 minutes before each RT fraction. Participant in a sitting position Arm 2: RT alone (control)
Outcomes	GI toxicity: Acute WHO classification QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT and up to 2 weeks post-RT
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to undergo radiotherapy or radiotherapy supported with subcutaneous administration of amifostine, according to a table of random numbers (0 v 1)."
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement. "Patients were randomly assigned to undergo radiotherapy or radiotherapy supported with subcutaneous administration of amifostine, according to a table of random numbers (0 v 1)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control was RT alone, no placebo

Koukourakis 2000 (*Continued*)

Blinding of outcome assessment	High risk	Control was RT alone, no placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Unclear risk	Protocol not seen and few expected outcomes reported
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	High risk	High risk overall

Kouloulias 2005

Methods	Design: Phase II multicentre randomised study Country: Greece Accrual dates: December 2002 to June 2003 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 54 Inclusion criteria: Karnofsky performance status 70 and were referred for radical RT (prostate, or stages IIB - III cervix uteri cancer) or postoperative RT (stages IB - II cervical corpus). All participants provided written informed consent Exclusion criteria: Previously treated with RT or chemotherapy or with haemoglobin levels 11 g/dL or with white blood cell counts 2500/ L and platelet counts 100,000/ L were excluded. Patients with major heart, lung, liver, renal, or neurologic/psychiatric disease and patients with haematologic malignancies were also excluded. Patients with hypertension controlled with medication were eligible for inclusion in the protocol. No modification of the antihypertensive regimen was done. Patients with clinically-evident pulmonary insufficiency (exertional dyspnoea) were excluded. Patients with serum creatinine or liver enzyme serum levels 1.5 and 2.5 times the normal value, respectively, were excluded Gender: 43.4% male Age: Intervention: 61.6 (8.5), Control: 61.3 (9.2) Type of cancer: Endometrial (15/53), cervical (14/53), prostate (24/53) Radiotherapy regimen received: 50 Gy to 72 Gy (depending on site) standard fractionation Primary/adjuvant/other: Primary and adjuvant Other treatment received: Patients with gynaecologic tumours also underwent brachytherapy as a boost
Interventions	Comparison: Amifostine topical intrarectal vs Amifostine subcutaneous application Arm 1: 1500 mg of amifostine was administered intrarectally as an aqueous solution in 40 mL of enema,. administered 20 - 30 mins before RT, and the participant remained in the bed for 2 mins thereafter to ensure the drug remained in the rectum. Amifostine was administered for all the days of treatment Arm 2: Pretreated with 5 mg of oral tropisetron 1 hour before the injection of amifostine.

	Amifostine (500 mg flat dose) was diluted in 5 mL of normal saline and was injected subcutaneously. The injection was repeated daily, 20 - 30 mins before each radiation fraction. Amifostine was injected with the patient in the supine position
Outcomes	GI toxicity: Acute RTOG QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT and up to 4 weeks post-RT ?
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Topical intrarectal versus subcutaneous application
Blinding of outcome assessment	Low risk	"To minimize bias, the rectal toxicity was evaluated using two toxicity scales by two independent observers. These physicians were unaware of the randomization arm for each case evaluated."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent attrition
Selective reporting (reporting bias)	Unclear risk	Protocol not seen but expected outcomes were reported
Other bias	Unclear risk	Groups A and B are interchangeably reported as having 26 and 27 participants
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Kouvaris 2003

Methods	Design: Phase II randomized study Country: Greece Accrual dates: June 2000 to January 2001 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 47 (36 analysed) Inclusion criteria: WHO performance status ≤ 1 and were referred for radical RT (prostate and cervical carcinoma) or postoperative RT (endometrial carcinoma). Written informed consent was obtained from all participants. Those with hypertension controlled with medication were included in the protocol without modification of their antihypertensive regimen Exclusion criteria: Patients previously treated with RT or chemotherapy or with haemoglobulin levels < 11 g/dl or WBC counts < 2500/μl and platelet counts < 100,000/μl; patients with major heart, lung, liver, renal, or neurologic/ psychiatric disease, and patients with hematologic malignancies; patients with clinically-evident pulmonary insufficiency (exceptional dyspnoea); patients with serum creatinine or liver enzyme serum levels > 1.5 and 2.5 times the normal values, respectively Gender: 44.44% male Age: Intervention: 61.33 (8.79), Control: 61.11 (8.58) Type of cancer: Prostate (16/36), cervical (11/36), endometrial (9/36) Radiotherapy regimen received: 50 Gy to 68 Gy standard fractionation Primary/adjuvant/other: Primary Other treatment received: All participants in this study received antiemetics as prophylactic therapy. All participants were pretreated with 5 mg of oral tropisetron (Navoban®; Novartis Pharmaceuticals Corp) 1 hour before every injection of amifostine
Interventions	Comparison: Amifostine vs control Arm 1: Amifostine (500 mg flat dose) was diluted in 50 ml of normal saline and injected intravenously over 6 mins. The injection was repeated daily, 20 - 30 mins before each RT fraction. Amifostine was injected with the participant in a supine position. Blood pressure was monitored before and 4 times during i.v. administration as well as within 15 mins after injection Arm 2: RT alone
Outcomes	GI toxicity: Acute WHO EORTC/RTOG QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: 12 months
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement

Kouvaris 2003 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment	Low risk	"In order to minimize any investigator-related bias, three independent physicians scored the radiation-induced acute rectal toxicity by using three different toxicity scales, respectively."
Incomplete outcome data (attrition bias) All outcomes	High risk	47 randomised but only 36 analysed.
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Kozelsky 2003

Methods	Design: Phase III, randomised, double-blind trial Country: USA Accrual dates: February 1998 and October 1999 Trial Reg.: NR Funding source: This study was conducted as a collaborative trial of the North Central Cancer Treatment Group and Mayo Clinic and was supported in part by Public Health Service grant nos. CA-25224, CA-37404, CA-15083, CA- 63826, CA-35195, CA-35103, CA-37417, CA-35415, CA-63849, CA-35101, CA-35269, and CA-63848
Participants	No. randomised: 129 Inclusion criteria: At least 18 years of age, histologically-confirmed adenocarcinoma or squamous cell carcinoma, had to receive pelvic RT at an NCCTG-approved radiation oncology facility, entire pelvis had to be encompassed by the planned RT fields. The superior border could not be superior to the L4 - 5 interspace or inferior to the most inferior aspect of the sacroiliac joints The total planned dose to the whole pelvic field had to be between 45 and 53.5 Gy (inclusive), with a daily dose of 1.7 to 2.1 Gy. A boost was allowed to the primary tumour or tumoir bed. Participants had to be entered onto study before the second RT fraction. Written informed consent and institutional review board approval were required before entry of any participant onto this study Exclusion criteria: Pregnant, had a known allergy to glutamine, had a history of pelvic RT, had any history of inflammatory bowel disease, were incontinent of stool, had a prior abdominal-perineal resection, or had planned use of leucovorin or cytotoxic chemotherapeutic agents concurrent with RT, other than FU Gender: 68.2% male

	Age: Intervention: 67.5 (mean), Control: 65.4 (mean) Type of cancer: Rectal, prostate, gynaecologic, other Radiotherapy regimen received: Total dose bt 45 and 60 Gy, daily dose of 1.7 to 2.1 Gy Primary/adjuvant/other: Primary Other treatment received: NR
Interventions	Comparison: Glutamine vs placebo Arm 1: Glutamine 4 g (8 mL) twice a day (morning and evening) 7 days a week during RT and for 2 weeks thereafter Arm 2: Identical-appearing placebo (glycine), which was administered according to the same schedule
Outcomes	GI toxicity: Acute NCI CTC QoL: UNISCALE QOL Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT, 4 weeks post-RT and at 12 and 24 months
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients were randomly assigned, in double-blind manner… glutamine…. Or an identical appearing placebo"
Blinding of outcome assessment	Low risk	"Patients were randomly assigned, in double-blind manner… glutamine…. Or an identical appearing placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"There were no differences between the two patient groups"
Selective reporting (reporting bias)	Unclear risk	Protocol not seen but few expected outcomes reported and little usable data
Other bias	Low risk	None noted
Overall judgement	Unclear risk	Based on methodological uncertainties above

Lips 2011

Methods	Design: Double-blind placebo-controlled randomized clinical trial Country: The Netherlands Accrual dates: December 2008 to February 2010 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 92 Inclusion criteria: Patients with prostate cancer scheduled for IMRT using fiducial markers for position verification Exclusion criteria: Severe constipation, kidney stones, heart block, abdominal diseases (Crohn's disease, colitis ulcerosa, diverticulitis), severe renal failure or creatinine clearance of < 50 mL/min/1.73 m^2, or a history of extensive abdominal surgery. Patients were not eligible if they used laxatives, tetracyclines, digoxin, iron, or ciprofloxacin Gender: Male Age median (range): Intervention: 70.5 (65 - 73.3), Control: 71 (67.8 - 75) Type of cancer: Prostate Radiotherapy regimen received: 77 Gy fractionated Primary/adjuvant/other: Primary Other treatment received: The pretreatment use of medication included mainly cardiovascular medicines such as statins, antihypertensive drugs, and anticoagulants; medicines for treatment of benign prostatic hyperplasia; antidiabetic drugs; and hormonal treatment
Interventions	Comparison: Magnesium oxide vs placebo Arm 1: 2 capsules of 250 mg magnesium oxide twice a day (a total dose of 1000 mg per day) during treatment Arm 2: 2 placebo capsules twice a day during treatment
Outcomes	GI toxicity: Acute CTCAE v 3.0 QoL: EORTC Other review outcomes: NR Other study outcomes: Secondary outcome measures included quality of life and acute toxicity Duration of follow-up: During and up to 4 weeks after RT
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-randomised "using the DESIGN computer program"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The placebo capsules were visually identical" "The boxes with capsules were randomized using the DESIGN computer

Lips 2011 (*Continued*)

		program, after which the Department of Pharmacy delivered the boxes blinded to the Department of Radiotherapy"
Blinding of outcome assessment	Low risk	"The placebo capsules were visually identical" "the Department of Pharmacy delivered the boxes blinded to the Department of Radiotherapy. Thus, the patient, the attending physician, and the investigator were blinded to the patient's treatment. "
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Low risk	Protocol not seen but expected outcomes were reported
Other bias	Low risk	None noted
Overall judgement	Low risk	Reasonable-quality study

Ljubenkovic 2002

Methods	Design: RCT Country: Yugoslavia Accrual dates: NR - study published in 2002 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 183 Inclusion criteria: NR Exclusion criteria: NR Gender: Female Age: NR Type of cancer: Cervix Radiotherapy regimen received: EBRT regimen not reported. Average high-dose volume overall was 5752 ± 1047 cm^3: 3360 - 8721 cm^3 for the experimental group and 4080 - 8874 cm^3 for the control group Primary/adjuvant/other: NR Other treatment received: Brachytherapy was administered with RALT technique in both groups
Interventions	Comparison: RT with special positioning table vs standard RT delivery Arm 1: RT under special conditions on a unique patient-table designed to reduce small bowel exposure Arm 2: RT under standard conditions

Ljubenkovic 2002 (*Continued*)

Outcomes	GI toxicity: Acute diarrhoea (EORTC/RTOG) QoL: NR Other review outcomes: Medication use Other study outcomes: Dosimetric parameters Duration of follow-up: NR
Notes	Baseline characteristics were not reported It was reported that "Individual application of exclusion techniques led to the protection of over 50% of the small bowel (118-1065 cm3) in 30/43 (70%) patients, and in 10/43 (23%) even more than 90% of the small bowel was protected (118-835 cm3), which would otherwise be irradiated with conventional techniques."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation not reported - just states that "(patients) were divided into two groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	High risk	Not blinded and investigators had designed the table and assessment parameters (that differed according to experimental and control groups)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	High risk	Different (more) parameters were measured for the experimental than the control groups. In the text, reference to control and experimental groups sometimes appeared to be switched, making the report very confusing. Reporting lacked detail, and method and timing of outcome assessments were not reported. Baseline characteristics were not reported
Other bias	High risk	"Our unique patient table was manufactured at our special demands…" suggests that the investigators might be considerably biased in this unblinded study

Ljubenkovic 2002 (*Continued*)

Overall judgement	High risk	Many limitations in study design and reporting

Maggio 2014

Methods	Design: Phase 2, multicentre, randomised, double-blind, placebo-controlled, dose-finding, 4-arm parallel-group trial Country: Italy Accrual dates: September 2006 to February 2008 Trial Reg.: EudraCT Number: 2006-000329-78 Funding source: Promefarm S.R.L. (EudraCT Number: 2006-000329-78, Sponsor Protocol Number: PMF603-PA1/06)
Participants	No. randomised: 166 Inclusion criteria: Clinically-localised prostate cancer with indication for radical RT, histologically-confirmed adenocarcinoma of the prostate, 3DCRT, and conventional fractionation (1.8 - 2.0 Gy/fraction) Exclusion criteria: Total International Committee on Radiation Units and Measurements (ICRU) dose < 70 Gy, life expectancy < 5 years, serious systemic disease (eg, insulin-treated diabetes mellitus), serious colonic disease (inflammatory bowel disease), patients undergoing pelvic radiation, prior chemotherapy or pelvic radiation, distant metastases (M), previous or current psychiatric illness, major rectal surgery or anorectal disease, active anal fissures, anorectal fistulas, previous anal sphincterotomy, and grade 3 - 4 haemorrhoids Gender: Male Age: NR Type of cancer: Prostate Radiotherapy regimen received: 70 Gy fractionated Primary/adjuvant/other: Primary Other treatment received: Hormonal therapy
Interventions	Comparison: 3 different sodium butyrate enemas vs placebo Arm 1: sodium butyrate enema 1 g daily Arm 2: sodium butyrate enema 2 g daily Arm 3: sodium butyrate enema 4 g daily Arm 4: Placebo enema Administered half shortly after the RT session and the second half at an interval of 8 to 12 hours
Outcomes	GI toxicity: Acute RTOG/EORTC QoL: NR Other review outcomes: NR Other study outcomes: Rectoscopy was worse in area or degree than at week 0; rectoscopy worse in degree and area > 4 - 8 cm than at 0 wk Duration of follow-up: 6 weeks after RT
Notes	

Maggio 2014 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Low risk	"Each center obtained 2 separated randomization lists, 1 for patients receiving ADT and the other for patients not receiving ADT, to balance the presence of ADT across the groups."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Even in per protocol population data from 95% of participants were available
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	No other issues.
Overall judgement	Unclear risk	Some limitations in reporting of methods such that risk of bias could not be fully assessed

Manikandan 2015

Methods	Design: RCT Country: India Trial Reg.: NR Accrual dates: NR Funding source: NR
Participants	No. randomised: 20 Inclusion criteria: Iintermediate and high-risk prostate cancer (T2b - T3b) Exclusion criteria: NR Gender: Male Type of cancer: Prostate Primary RT/adjuvant RT/other: Primary Other treatment received: Neo-adjuvant, concurrent and adjuvant hormone therapy

Manikandan 2015 (*Continued*)

Interventions	Comparison: HDR BT vs IMRT Arm 1: HDR BT: 19 Gy in 2 fractions via an implant Arm 2: IMRT: 29 Gy in 15 fractions over 3 weeks All participants received IMRT 45 GY in 25 fractions over 5 weeks in the initial phase of the study (phase 1)
Outcomes	GI Toxicity: Acute and late (scale NR) QoL: NR Other review outcomes: NR Other study outcomes: Dosimetric parameters and genito-urinary toxicity Duration of follow-up: Toxicity was assessed at the end of phase 1, end of phase 2 and 1, 3, and 6 months after completion of treatment
Notes	Conference abstracts only, therefore minimal usable data. Significantly lower mean radiation doses to rectum and bladder were reported with HDR BT compared with IMRT. Grade 2 or more acute genito-urinary toxicity occurred in 4/10 participants in the HDR BT arm and 5/10 in the IMRT arm. In a subsequent conference presentation the sample size included 30 participants but we could not extract data from this report - await full trial report. Emailed 18 January 2017 but no response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement.
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Manir 2014

Methods	Design: Phase 3, double-blind, RCT Country: India Accrual dates: December 2011 to April 2013 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 91 Inclusion criteria: Aged 18 - 75, histologically-confirmed squamous or adenocarcinoma Exclusion criteria: Inflammatory bowel disease, prior abdomino-perineal resection, history of prior RT, pregnancy and severe comorbidities Gender: 34% male Mean age (SD): Intervention: 57.2 (8.14), Control: 56.2 (9.6) Type of cancer: Pelvic malignancy squamous or adenocarcinoma (58.1% cervix, 18.6% rectum) Radiotherapy regimen received: 45 Gy - 50 Gy in standard fractionation Primary/adjuvant/other: Primary and adjuvant Other treatment received: With or without concurrent chemotherapy (85% with)
Interventions	Comparison: Glutamine vs placebo Arm 1: 10 g glutamine granules dissolved in 100 ml of fruit juice given 1 hour before radiation Arm 2: Placebo (glycine) granules dissolved in 100 ml of fruit juice given 1 hour before radiation
Outcomes	GI toxicity: Acute CTCAE v 4.02 QoL: NR Other review outcomes: NR Other study outcomes: Enteritis, proctitis Duration of follow-up: 6 weeks during RT and 1 week post-RT
Notes	Delay in RT (< 7 days) in case of 87% of participants

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind placebo controlled"
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition (< 20%)

Manir 2014 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Mansouri-Tehrani 2016

Methods	Design: 3-arm randomised placebo-controlled trial Country: Iran Accrual dates: October 2013 to May 2013 Trial reg: IRCT2015030421338N1 Funding source: Zist Takhmir Company - probiotics and placebo; Allas Company - honey; University of Isfahan grant funded the research
Participants	No. randomised: 78 (67 analysed) Inclusion criteria: adults undergoing pelvic RT Exclusion criteria: Opioid use, antimicrobila treatment, presence of any acute or chronic gastrointestinal condition associated with diarrhoea for at least 1 month before recruitment Gender: 58.2% male Age: 20 to 85 years (mean 62 years, SD = 14.8 years) Type of cancer: Colorectal (24/67); prostate (15/67); endometrial (10/67); bladder (8/67); ovary (4/67); cervical 4/67); bone sarcoma (2/67) Radiotherapy regimen received: Total dose of 4000 - 5000 cGy (1.8 Gy/fraction) delivered on 5/7 days per week for 4 - 5 weeks Other treatment: CT/RT received by 26/67 participants with rates across groups as follows: 11.9% (Probiotic group); 13.4% (Probiotic + honey group); 13.4% (Placebo group)
Interventions	Arm 1: Probiotics (LactoCareO) - 2 capsules a day comprising: Lactobacillus casei (1.5 x 109 CFU); Lactobacillus acidophilus (1.5 x 1010 CFU); Lactobacillus rhamnosus (3.5 x 109 CFU); Lactobacillus bulgaricus (2.5 x 108 CFU); Bifidobacterium breve (1 x 1010 CFU); bifidobacterium longum (5 x 108 CFU); Streptococcus thermophilus (1.5 x 108 CFU) per 500mg. 1 capsule in the morning and 1 in the evening following 150 g low-fat yoghurt Arm 2: Probiotic (LactoCareO) as above, plus 15 g honey in the morning and evening Arm 3: Placebo capsules taken after 150 g low-fat yoghurt Interventions began 1 week prior to and for the duration of RT treatment. All groups received list of allowed and prohibited foods and a low-fat yoghurt
Outcomes	GI toxicity: Diarrhoea (CTCAE v2.0) Other review outcomes: Medication for symptom control Other study outcomes: Stool frequency and consistency (Bristol scale) Duration of follow-up: During RT only
Notes	Authors concluded in the abstract that "Probiotics with or without honey can reduce the incidence of radiation-induced diarrhea and the need for antidiarrheal medication."

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Simple randomisation was used to allocate patients to three groups..."
Allocation concealment (selection bias)	Unclear risk	Authors do not state method of concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded to probiotic or placebo allocation
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	11 (14%) of the original 78 participants recruited were excluded due to failure to follow up. Time points at which these participants dropped out are not reported, nor their original group allocation; it is just stated that "11 patients were excluded for failure to follow-up"
Selective reporting (reporting bias)	Unclear risk	The primary outcome data (diarrhoea according to CTCAE criteria) are not clearly reported. "Moderate to severe diarrheal symptoms (grades 2, 3) was recorded in 31 (46.3%) patients during pelvic radiotherapy. The number (percentage) patients with diarrhea grades 2 and 3 was 7 (31.8) , 4 (19) and 17 (70.8)..." These numbers do not add up to 31. Authors were contacted for clarity but no response had been received at the time of writing Medication for symptom control was reported as percentages rather than precise data
Other bias	Unclear risk	Baseline group characteristics were similar but there was some variation in the types of cancer across groups
Overall judgement	Unclear risk	Primary outcome not reported, quantity of evaluable data not reported, attrition rates assumed to be zero but not reported. 11 patients (of the 78 originally recruited) were excluded for "failure to follow-up"

		but no statement on which group(s) these were originally allocated - no CONSORT flowchart provided

Mariados 2015

Methods	Design: Multicentre single-blind RCT Country: USA Accrual dates: January 2012 to April 2013 Trial Reg.: NR Funding source: Augmenix, Inc
Participants	No. randomised:222 (219 analysed) Inclusion criteria: Men with stage T1 or T2 prostate cancer, a Gleason score of ≤ 7, a PSA concentration of ≤ 20 ng/mL, and a Zubrod performance status 0 to 1, who were planning to undergo IG-IMRT Exclusion criteria: Prostate volume of > 80 cm^3, extra capsular extension of disease or > 50% positive biopsy cores, metastatic disease, indicated or recent androgen deprivation therapy, and prior prostate surgery or RT Gender: Male Age: Intervention 66.4 and Control 67.7 years Type of cancer: Prostate Radiotherapy regimen received: IG-IMRT 79.2 Gy in 1.8-Gy fractions Other treatment received: Antibiotic prophylaxis was administered prior to fiducial or fiducial and spacer procedure 95% of the time, anaesthesia, sedation
Interventions	Comparison: Hydrogel spacer vs no spacer Arm 1: Transperineal injection of absorbable hydrogel spacer (and fiducial marker placement) Arm 2: No transperineal injection (fiducial marker placement only)
Outcomes	GI toxicity: Acute and late (CTCAE v4) QoL: Yes (Expanded prostate cancer index composite) Other review outcomes: NR Other study outcomes: Other toxicity Duration of follow-up: Primary end points were reported at a median of 15 months with a further follow-up report at a median of 3 years. Assessed at baseline and 3, 6, 12, and 15 months
Notes	Baseline characteristics were comparable between study arms, including age, race, weight, height, BMI, stage, PSA, prostate volume and other parameters MRI scans at 12 months verified spacer absorption. Authors concluded in the primary paper that "Overall safety of the spacer seemed to be excellent, with no device-related AEs and no rectal infections, rectal complications, and other AEs" Hamstra 2017 reported follow-up data at a median of approximately 3 years. However some of the institutions did not participate in this follow-up protocol, therefore only 63% of the original participants contributed data to the 3-year report

Mariados 2015 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"immediately randomized (envelope opened)" - insufficient details to make a judgement Randomization ratio was 2:1
Allocation concealment (selection bias)	Unclear risk	"envelope opened" - allocation concealment is not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was a single-blind RCT, with participants "blinded to treatment randomization"
Blinding of outcome assessment	Low risk	All AEs were recorded "blinded to treatment randomization"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Low attrition in the primary paper- 219/222 participants evaluated. However, only 63% of participants contributed data to the follow-up paper (Hamstra 2017). Institutional participation in the extended follow-up protocol was voluntary and the reasons for these institutions choosing not to participate are not given
Selective reporting (reporting bias)	Unclear risk	Data in the primary paper and the follow-up report (Hamstra 2017) are given as percentages in most instances and the precise data (numerators and denominators) are unclear
Other bias	High risk	Conflict of interest: 2 of the authors (NM and DS) are Augmenix shareholders. JS has received speaking honoraria from Augmenix
Overall judgement	Unclear risk	Due to factors above

Martenson 1996

Methods	Design: Randomised, double-blind trial Country: USA Accrual dates: August 1993 to February 1994 Trial Reg.: NR Funding source: Study was supported in part by Pub Health Service grants CA-25224, CA-37404, CA-15083, CA-35269, CA-??101, CA-52352, CA-37417, CA-35272, and CA-35103 from National Cancer Institute; olsalazine and placebo provided by Pharmacia, Piscataway, NJ
Participants	No. randomised: 62 Inclusion criteria: Current or previous histologic proof of cancer in the pelvis without metastases beyond regional lymph nodes, in whom a course of continuous external beam pelvic RT was planned Exclusion criteria: No systemic administration of cytotoxic chemotherapy was allowed; patient lacked a functioning rectum, they had stool incontinence, stool frequeny was ≥ 6 per day, or if irradiation of the entire perineum was planned. History of prior pelvic radiation therapy, inflammatory bowel disease, known salicylate allergy, or active intraluminal bowel tumours, or patients whose ECOG performance status was 3 or 4 (inactive > 50% of the day); pregnancy or lactation in case of women Gender: 79.3% male Age: Intervention: 68.1 (mean), Control: 69.8 (mean) Type of cancer: Mainly prostate cancer (74%) Radiotherapy regimen received: Daily dose, specified at isocenter or midplane, had to be 1.7 - 2.1 Gy (inclusive); total pelvic dose 45 - 53.5 Gy (inclusive) Primary/adjuvant/other: Primary Other treatment received: Allowed: 5-FU with or without levamisole (10.3%)
Interventions	Comparison: Olsalazine vs placebo Arm 1: 250 mg olsalazine, 2 capsules twice daily Arm 2: Identical-appearing placebo, 2 capsules twice daily
Outcomes	GI toxicity: Acute NCIT criteria QoL: (scale used) NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT (duration not given)
Notes	Participant accrual was stopped early, immediately after a preliminary analysis of the data suggested excessive diarrhoea in those who had been randomised to receive olsalazine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was do at the North Central Cancer Treatment Group's (NCCTG) Operations Office"
Allocation concealment (selection bias)	Low risk	"Double-blind fashion"

Martenson 1996 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind fashion"
Blinding of outcome assessment	Low risk	"Double-blind fashion"
Incomplete outcome data (attrition bias) All outcomes	High risk	"The study was closed early, after entry of 58 evaluable patients, when a preliminary analysis showed excess diarrhea in patients randomized to olsalazine."
Selective reporting (reporting bias)	High risk	"The study was closed early, after entry of 58 evaluable patients, when a preliminary analysis showed excess diarrhea in patients randomized to olsalazine."
Other bias	High risk	"The study was closed early, after entry of 58 evaluable patients, when a preliminary analysis showed excess diarrhea in patients randomized to olsalazine."
Overall judgement	High risk	High risk overall

Martenson 2000

Methods	Design: RCT Country: USA Accrual dates: April 1996 to May 1997 Trial Reg.: NR Funding source: Public Health Service grants no. CA-25224, CA-37404, CA-35269, CA-35103, CA-35195, CA-63849, CA-37417, CA-63848, CA-35448, CA-35415, CA-35101, CA-35113, CA-52352, and CA-35272 from the National Cancer Institute Department of Health and Human Services, Bethesda, MD
Participants	No. randomised: 128 Inclusion criteria: Patients with current or previous histologic proof of cancer in the pelvis without distant metastases and who were to receive a course of planned continuous external pelvic RT. Women of childbearing potential had to agree to use contraception before entry onto the study Exclusion criteria: Patients with a known allergy to sucralfate, a history of inflammatory bowel disease, chronic renal failure, stool frequency of 7+ episodes per day, or stool incontinence; ECOG performance status of 3 or 4, active intraluminal gastrointestinal tumours, or a previous history of pelvic RT; Pregnant or lactating women Gender: 64% male Age: NR Type of cancer: Cancer in the pelvis without distant metastases Radiotherapy regimen received: 45 Gy to 53.5 Gy fractionated Primary/adjuvant/other: Primary

Martenson 2000 (*Continued*)

	Other treatment received: 10 to 12 months after completion of pelvic RT
Interventions	Comparison: Sucralfate vs placebo Arm 1: Sucralfate (500 mg, 3 capsules every 6 hours) Treatment with sucralfate or placebo was discontinued if grade 3 diarrhoea or worse occurred Arm 2: Placebo (microcrystalline cellulase capsules, 3 capsules every 6 hours); Treatment with sucralfate or placebo was discontinued if grade 3 diarrhoea or worse occurred
Outcomes	GI toxicity: Acute NCIT criteria QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: 10 to 12 months after completion of pelvic RT
Notes	Participant-reported symptoms in Table 4 which shows that more patients in the sucralfate group used protective clothing or pads to prevent soiling than in the control group (23% vs 8%; P = 0.04)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Low risk	No concern
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported
Selective reporting (reporting bias)	Low risk	Protocol not seen but expected outcomes reported
Other bias	Low risk	None noted
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Martenson 2008

Methods	Design: Phase III, double-blind study Country: USA Accrual dates: May 2002 to October 2005 Trial Reg.: NCT00033605 Funding source: Public Health Service Grants No. CA-60276, CA-35101, CA-35103, CA-35415, CA-35431, CA-63849, CA-35269, CA-35119, CA-37417, CA-35267, CA-52654, and CA-35195. Supplementary funding and medications were provided by Novartis (Basel, Switzerland)
Participants	No. randomised: 130 Inclusion criteria: Histologic proof of cancer in the pelvis (without distant metastases) who were scheduled to receive a continuous course of RT, either as definitive treatment or in an adjuvant setting; Patients treated concurrently with pelvic and para-aortic RT Exclusion criteria: Allergy to octreotide, inflammatory bowel disease, renal failure, grade 3 or higher diarrhoea before study entry, ECOG performance status of 3 or 4, planned concurrent radiation therapy and cytotoxic chemotherapy (other than with fluorouracil or cisplatin), planned brachytherapy before completion of external RT, lack of a functional rectum, and faecal incontinence. Women with childbearing potential were required to use effective contraception, and pregnant or nursing women were excluded from the study Gender: NR Age: NR Type of cancer: Rectum, prostate, gynaecologic Radiotherapy regimen received: 45.0 Gy - 53.5 Gy in standard fractionation Primary/adjuvant/other: Primary Other treatment received: Cisplatin (14%), Leucovorin (8%), Fluorouracil (39%)
Interventions	Comparison: Octreotide acetate vs placebo Arm 1: Day 1: 100 ug, administered subcutaneously, Day 2 If participant had no signs of toxicity after the initial injection, they received depot octreotide (20 mg, administered intramuscularly); second intramuscular injection of octreotide (20 mg) was administered on day 29 (not given in case of severe side effects) Arm 2: Placebo injection
Outcomes	GI toxicity: Acute NCIT criteria, v. 2.0.3 QoL: NR (median) Other review outcomes: NR Other study outcomes: NR Duration of follow-up: 8 weeks during RT
Notes	A significantly higher number of patients with a history of rectal surgery or primary rectal cancer were included in the placebo arm of the study. These imbalances potentially could cause more bowel problems for participants in the placebo group; more participants in placebo group received fluorouracil in continuous infusion than in the intervention arm (41% vs 27%)

Risk of bias

Bias	Authors' judgement	Support for judgement

Martenson 2008 (*Continued*)

Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned in a double-blind fashion to receive octreotide or the placebo." This appears to have been done centrally
Allocation concealment (selection bias)	Low risk	"The operations office of the NCCTG, in Rochester, MN, was the randomization center for this study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment	Unclear risk	Double-blind; "Patients were randomly assigned in a double-blind fashion to receive octreotide or the placebo."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Toxicity data from all participants included in analysis of primary end point; 4% refused protocol treatment after random allocation
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	"significantly greater number of patients with rectal cancer / surgery" and more participants receiving fluorouracil in the placebo arm - this baseline imbalance could cause more bowel problems in the placebo arm
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Martin 2002

Methods	Design: Double-blind randomised trial Country: Germany Accrual dates: March 1994 to June 1997 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 56 Inclusion criteria: Patients with a proven indication for adjuvant external beam therapy of the pelvic after macroscopically complete resection of a pelvic malignancy, age > 18 years and given informed consent before starting treatment. All patients had a Karnofsky inde of 905 and above Exclusion criteria: Palliative indications for pelvic irradiation, existence of a colostomy, known intolerance to proteolytic enzyme preparations or to contents of the study med-

	ication and participation in other clinical studies within the last 30 days Gender: 23.21% male Age: Intervention: 52.8, Control: 57.3 Type of cancer: rectosigmoid, endometrial, vulva, prostate, other Radiotherapy regimen received: 50.4 Gy in standard fractionation Primary RT/adjuvant RT/other: Adjuvant Other treatment received: NR
Interventions	Comparison: proteolytic enzymes vs placebo Arm 1: 3 x 4 capsules of the study medication daily, starting 3 days before RT and finishing on the last day of RT. WOBE-MUGOS capsules containing 100 mg papain (270 FIPE), 40 mg trypsin (29 ukat) and 40 mg chymotrypsin (200 ukat) Arm 2: Placebo capsule of identical design without any enzyme contents
Outcomes	GI Toxicity: Acute, CTC / RTOG - Diarrhoea QoL: Fatigue score Other review outcomes: NR Other study outcomes: Secondary objectives were the number of supportive medications (29 in enzyme group, 19 in placebo group) and treatment interruptions due to acute toxicity (mean days: 2.44 in enzyme group and 1.46 in placebo group). 52 patients finished the entire RT as planned, 4 finished RT prematurely Duration of follow-up: During RT
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors state that 2 randomisation groups were generated using the prepared, closed and randomised study medication. Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Authors do not state method of concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded to intervention; study described as double-blind and thus study personnel are presumed to be blinded to intervention
Blinding of outcome assessment	Unclear risk	Not stated whether those study personnel obtaining data from participants or transcribing into severity codes were blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis was done on an ITT basis. However 8 (14%) participants withdrew at their own request before completing all assess-

Martin 2002 (*Continued*)

		ments
Selective reporting (reporting bias)	Low risk	The 5 prespecified toxicity outcomes are reported
Other bias	Low risk	No baseline characteristics table is provided. However, authors state that comparability of study groups was proven (Mann-Whitney). Cancer sites not evenly distributed between groups. Also a 10-day difference between groups between surgery and RT, but not clear what effect this may have had. Age and M:F ratio comparable
Overall judgement	High risk	No powering or primary end point specified. Study found no difference between groups in toxicity end points but impossible to determine whether the study was underpowered. Reasons for self-withdrawal from trial not reported. No CONSORT diagram provided

McGough 2008

Methods	Design: Randomised controlled study Country: UK Accrual dates: January 2005 to July 2005 Trial Reg.: NR Funding source: An unrestricted grant from SHS International (Liverpool, UK) supported some of the costs of this study and all the elemental diet cartons or sachets were provided for free by the manufacturer. In addition to receiving an unrestricted grant from SHS International, in 2005 Dr Andreyev acted as a paid consultant for Numico
Participants	No. randomised: 50 Inclusion criteria: Patients with a histologically-proven gynaecological, urological or lower gastrointestinal malignancy due for radical or adjuvant radiotherapy to the pelvis were eligible Exclusion criteria: NR Gender: 42% male Age: Intervention median (range): 62.5 (29 - 79), Control: 58 (38 - 82) Type of cancer: Endometrium (13), Cervix (7), Ovary (1), Bladder (2), Prostate (11), Rectum (9), Anus (4), Other (3) Radiotherapy regimen received: 50.4 Gy to 54 Gy in standard fractionation Primary/adjuvant/other: Primary Other treatment received: Some participants received concomitant chemotherapy
Interventions	Comparison: Elemental diet vs control Arm 1: Following an interview to establish habitual dietary patterns and to encourage

	compliance, participants in the intervention group were asked to replace 1 meal a day, equivalent to 33% of total caloric requirements, with elemental diet. A selection of E028 Extra (SHS International, Liverpool, UK) ready-to-drink 250 mL cartons and E028 Extra flavoured powder sachets were provided Arm 2: Habitual diet during RT
Outcomes	GI toxicity: RTOG QoL: IBDQ Other review outcomes: NR Other study outcomes: Faecal calprotectin Duration of follow-up: 10 weeks
Notes	At 1 month after treatment (week 10), 47 participants (94%) were available for follow-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The independent Institute of Cancer Research, Randomisation Office, randomised patients using permuted blocks
Allocation concealment (selection bias)	Low risk	The independent Institute of Cancer Research, Randomisation Office, randomised patients using permuted blocks
Blinding of participants and personnel (performance bias) All outcomes	High risk	Allocation group unblinded to participants and investigators
Blinding of outcome assessment	High risk	Allocation group unblinded to analysts
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed acute time points with 6% dropout at week 10
Selective reporting (reporting bias)	Low risk	All stated outcomes reported
Other bias	High risk	Poor compliance with interventional (elemental formula) prescription meant that dose consumed may not have been large enough to create an effect. Mean dose consumed in interventional group amounted to just 21% of caloric intake versus 33% planned. Relatively high LCT (fat) content of E028 may have masked effect of formula
Overall judgement	High risk	High risk overall

McGuffin 2016

Methods	Design: RCT Country: NR Accrual dates: NR Trial Reg.: NR Funding source: NR
Participants	No. randomised: 78 Inclusion criteria: Patients undergoing a radical course of RT to the prostate were eligible Exclusion criteria: NR Gender: Male Age: NR Type of cancer: Prostate Radiotherapy regimen received: NR Primary/adjuvant/other: Primary Other treatment received: NR
Interventions	Comparison: OvolTM vs control Arm 1: NR Arm 2: NR
Outcomes	GI toxicity: Acute NCI CTCAE v4.0 QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: NR
Notes	NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement

McGuffin 2016 (*Continued*)

Overall judgement	Unclear risk	Insufficient detail to make a judgement

Menander-Huber 1978

Methods	Design: Randomised,double-blind, plaebo-controlled study Country: Sweden and USA Accrual dates: NR Trial Reg.: NR Funding source: NR
Participants	No. randomised: 38 Inclusion criteria: Patients receiving radiation for bladder tumours Exclusion criteria: NR Gender: 81.6% male Age: NR Type of cancer: Bladder Radiotherapy regimen received: 6400 or 8400 rad with CRE factor 1800 or 1890 Primary/adjuvant/other: Primary Other treatment received: All participants received antibacterial therapy throughout trial and were permitted to use a specified anti-diarrhoeal as needed
Interventions	Comparison: Orgotein vs control Arm 1: 4 mg orgotein dissolved in about 1 ml USP saline injected subcutaneously 15 - 30 mins after completion of each daily radiation session Arm 2: 4 mg placebo dissolved in about 1 ml USP saline injected subcutaneously 15 - 30 mins after completion of each daily radiation session
Outcomes	GI toxicity: NR QoL: (scale used) NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT and at 4 months and 2 years
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo controlled

Menander-Huber 1978 (*Continued*)

Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Miller 2016

Methods	Design: Double-blind, parallel arm RCT Country: USA Accrual dates: April 2011 and May 2013 Trial Reg.: NCT01198145 Funding source: The study was funded by the US National Institutes of Health grant CA 124477. The research for North Central Cancer Treatment Group N08C9 (Alliance) was supported, in part, by grants from the NCI to the Alliance for Clinical Trials in Oncology (Monica M. Bertagnolli, MD,Chair) (CA31946) and to the Alliance Statistics and Data Center (Daniel J.Sargent, PhD) (CA33601). The study agent was provided by Pfizer. Mayo Clinic paid for preparation of the study placebo
Participants	No. randomised: 87 (84 analysed) Inclusion criteria: Patients undergoing pelvic RT Exclusion criteria: Gender: 61% male Age median (range): Intervention: 59 (37 - 84), Control: 56.5 (37 - 81) Type of cancer: Colon and/or rectal (50/84), Prostate (15/84), Endometrial (11/84), other (8/84) Radiotherapy regimen: Patients were required to receive a planned dose of 45.0 to 53.5 Gy to the pelvis that included at least the posterior pelvis with conventional fractionation (1.7 - 2.1 Gy once daily) Other treatment received: Concurrent chemotherapy in 63/84
Interventions	Comparison: Sulfasalazine vs placebo Arm A: Oral sulfasalazine twice daily during RT and for 4 weeks after completion of RT Arm B: Oral placebo twice daily during RT and for 4 weeks after completion of RT
Outcomes	GI toxicity: Primary: maximum severity of diarrhoea toxicity (by CTCAE v4.0) during and after RT (up to 6 weeks post RT) Secondary: maximum severity and the duration of maximum severity of each outcome variable (i.e. rectal bleeding, abdominal cramping, tenesmus, constipation, and diarrhoea) measured during and after RT; area under the curve that combines the individual severity of diarrhoea toxicity as measured by the CTCAE v4.0 during and after RT; percentage of participants in each arm that experience each outcome variable during and after RT (up to 6 weeks post-RT); long-term diarrhoea severity grade; bowel function

	score; percentage of participants in each arm that recorded "yes" to each of questions 2 - 12 on the bowel function questionnaire; percentage of participants in each arm that require any and each type of antidiarrhoeal medications; percentage of participants in each arm that experience clinically-significant deficits in overall quality of life and fatigue (up to 24 months post-RT) Duration of follow-up: RT and 6 weeks after RT
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed through the Clinical Trials Support Unit with stratification"
Allocation concealment (selection bias)	Low risk	"Patients were assigned to receive either sulfasalazine (arm 1) or placebo (arm 2) in a 1:1 ratio with an algorithm used routinely in clinical trials of the research alliance on the basis of the Pocock and Simon dynamic allocation method "
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The identity of the study agents was masked to patients and medical providers before dispensing from the site pharmacy."
Blinding of outcome assessment	Low risk	"The identity of the study agents was masked to patients and medical providers before dispensing from the site pharmacy."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"three patients were excluded from the analyses because of cancellations or protocol violations."
Selective reporting (reporting bias)	Low risk	Protocol not seen but expected outcomes reported. ITT analysis
Other bias	Low risk	6 participants in the placebo arm and 17 in the intervention arm did not receive the allocated treatment. In the intervention arm, this included 9 due to adverse events. These participants were appropriately included in the ITT analyses
Overall judgement	Low risk	High-quality study

Muecke 2010

Methods	Design: Mulitcentre, phase III randomised trial Country: Germany Accrual dates: January 2000 to June 2006 Trial Reg.: NR Funding source: Supported by a grant from biosyn Arzneimittel GmbH, Fellbach, Germany
Participants	No. randomised: 108 Inclusion criteria: Patients with histopathologically-confirmed carcinomas of the cervix or corpus uteri with a significant whole-blood selenium deficiency (i.e. concentration < 85 mg/L) after curative surgical treatment Exclusion criteria: Patients with metastatic disease, diarrhoea before RT, radiochemotherapy, or supplementation of selenium before RT, as well as patients who had undergone previous pelvic RT Gender: Female Age median (range): Intervention: 64.8 (37 - 80), Control: 63.8 (31 - 80) Type of cancer: Cervical and uterine Radiotherapy regimen received: External RT was delivered with a 6- to 18-MV linear accelerator. 5 fractions a week were planned Primary/adjuvant/other: Adjuvant Other treatment received: High-dose rate brachytherapy of the vagina was considered optional, in accordance with German evidence-based guidelines. Brachytherapy was delivered by iridium 192 afterloading
Interventions	Comparison: Selenium vs no intervention Arm 1: 500 mg of selenium by mouth on the days of RT and 300 mg of selenium on the days without RT Arm 2: No supplement (control)
Outcomes	GI toxicity: Acute CTC version 2 QoL: Visual analogue scale 10 (very good) to 0 (very bad) Other review outcomes: NR Other study outcomes: Postoperative whole-blood selenium value Duration of follow-up: After surgical treatment, during RT, at the end of RT, and 6 weeks after RT
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias)	High risk	No placebo used

Muecke 2010 (*Continued*)

All outcomes		
Blinding of outcome assessment	Low risk	"Randomization, data monitoring, and documentation were carried out and monitored by an independent person not directly involved in the patients' care. Thereby, an influence of the study investigator should be avoided."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Low risk	Protocol not seen but expected outcomes were reported
Other bias	Low risk	Baseline characteristics were similar across groups
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Mullaney 2014

Methods	Design: RCT Country: Ireland Accrual dates: 2007 to 2010 Trial Reg.: NR Funding source: St Lukes Institute of Cancer Research and the Health Research Board
Participants	No. randomised: 244 originally enrolled but institutional prehydration instructions were changed after interim analysis of the first 115 recruits and these participants were excluded from the analysis. Subsequently 127 were enrolled and 110 analysed Inclusion criteria: Karnofsky performance status of $\geq$ 60; radical prostate EBRT in the supine position, no history of urinary incontinence, catheterisation or previous surgery for urinary conditions except transurethral resection of the prostate, and provision of written informed consent Exclusion criteria: evidence of any significant clinical disorder that made it undesirable for the patient to participate or if it was felt that the patient could not comply with the protocol Gender: Male Type of cancer: Prostate Radiotherapy regimen received: 74 Gy in 37 fractions to the prostate and proximal or entire seminal vesicles (based on disease staging), using 3DCRT, in accordance with institutional standard practice Primary/adjuvant/other: Primary Other treatment received: NR
Interventions	Comparison: 540 mL vs 1080 mL water Arm 1: 540 mL water to drink after instructions

	Arm 2: 1080 mL water after instructions Instructions for both groups were: 1- void bladder; 2- consume the allocated water in 10 minutes; and 3- wait 30 - 40 minutes prior to the treatment planning computerised tomography (TPCT) and RT
Outcomes	GI toxicity: Acute and late (RTOG) QoL: Yes, related to bladder discomfort and urinary symptoms Other review outcomes: NR Other study outcomes: Bladder volume (BV) (visual analogue scale) Duration of follow-up: every 3 to 6 months up to 4 years
Notes	Baseline characteristics were comparable between study arms, including age, stage, and performance score. Bladder volumes achieved were consistently higher for the 1080 ml group. However, "there were were no statistically significant associations between arm and GU/GI toxicity, dose median comfort scores, or median QoL scores. The 540 mL bladder-filling arm resulted in reproducible bladder volumes throughout a course of RT, without any deterioration in QoL or increase in toxicities for prostate patients." Since the results of this trial have become available, institutional standard practice has changed to the 540 mL bladder-filling protocol for all prostate conformal RT patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"a computer-generated random number list prepared by an individual with no clinical involvement in the trial"
Allocation concealment (selection bias)	Low risk	"The allocation sequence was concealed from the researcher in sequentially numbered, opaque, sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Out of 244 consenting patients, 55 from intervention group (540 mL) and 62 from control (1080 mL) were excuded due to institutional hydration instructions. In the final 540 ml group, 10 were withdrawn; 6 due to prone positioning; 1 non-compliant; 1 failed bladder DVCs; 2 medical team request. In the 1080 ml group 7 were withdrawn: 5 due to change to prone positioning; 2 failed bladder DVCs

Mullaney 2014 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Protocol not seen, but methods and expected outcomes were clearly reported
Other bias	Unclear risk	"The interim analysis found that the institutional prehydration instructions (drink 1-2 L per day for 3 consecutive days prior to TPCT and first treatment) resulted in artificially large bladder volumes at TPCT that were not achievable on-treatment because patients failed to follow the instruction after the TPCT appointment. Consequently, the prehydration instructions were withdrawn for all prostate cancer patients. As a result of this institutional change these initial 115 patients were excluded from this analysis."
Overall judgement	Unclear risk	Half the sample size was excluded after modifying the institutional prehydration protocol

Murphy 2000

Methods	Design: Non-powered RCT, described as a 'pilot' trial by the authors Country: Canada Accrual dates: 18 months (start - end dates NR) Trial Reg.: NR Funding source: Proctor & Gamble Corporation provided partial funding of this studty through a research grant
Participants	No. randomised: 84 Inclusion criteria: Patients with prostate or gynaecologic cancer who were undergoing RT to the pelvis of at least 40 Gy in 20 fractions Exclusion criteria: History of gastrointestinal disease or who regularly used laxatives or anti-diarrhoea medications Gender: 85% male Age: Intervention: Male 63.7 (median) 50 - 79 (range), Female 56.3 (median) 46 - 76 (range), Control: Male 66.7 (median) 54 - 75 (range), Female 64.7 (median) 50 - 69 (range) Type of cancer: Prostate or gynaecologic Radiotherapy regimen received: Total prescribed dose not reported for the study but described usually comprising 1 teaspoon a day metamucil increasing to 2 teaspoons a day. Treatment regimen was most commonly 2Gy / day, 5 days a week for 4 to 5 weeks, followed immediately by 8 to 10 additional, conformal treaments Primary/adjuvant/other: Primary Other treatment received: NR

Interventions	Comparison: Psyllium (metamucil) plus low fibre (dose not reported), limited fat (dose not reported) and low alcohol and caffeine intake vs control low fibre (dose not reported) , limited fat (dose not reported) and low alcohol and caffeine intake Arm 1: Daily dose of metamucil (dose 1 - 2 teaspoons a day), taken prophylactically beginning with the start of RT. Some participants did not take it at the beginning, but used it as soon as symptoms started Arm 2: Non-metamucil group.
Outcomes	GI toxicity: Acute Murphy Diarrhoea Scale (unvalidated) QoL: NR Other review outcomes: NR Other study outcomes: Mean Severity Score (calculated from MDS); Incidence of diarrhoea; Mean time (days) to onset of diarhoea; Mean duation (days) of diarrhoea Duration of follow-up: During RT and 28 days post-RT
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random-number table used for allocation to treatment groups
Allocation concealment (selection bias)	Unclear risk	Unclear as to how easy it might have been for participants to guess their allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Allocation group unblinded to participants and investigators
Blinding of outcome assessment	High risk	Allocation group unblinded to analysts
Incomplete outcome data (attrition bias) All outcomes	High risk	28% of participants (24/84) excluded from final analysis due to incomplete or unreliable data, or protocol violation (e.g. using metamucil when in non-interventional group)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes seem to have been reported
Other bias	High risk	No powering statement and therefore impossible to judge significance of results. Main outcomes (incidence and severity of diarrhoea) assessed using a non-validated scale. Also, aim of the intervention is not clear: participants in the intervention

Murphy 2000 (*Continued*)

		group were allowed to take metamucil as a prophyactic OR as a therapy to control diarrhoea when occurring
Overall judgement	High risk	

Naik 2016

Methods	Design: Open parallel-arm RCT Country: India Trial Reg.: NR Accrual dates: Sept 2014 to August 2015 Funding source: Roentgen Oncologic Solutions PVt. Ltd was acknowledged but funding not directly attributed
Participants	No. randomised: 40 Inclusion criteria: Women requiring primary treatment of histologically-confirmed squamous cell cervical cance stage IIA to IVA; Karofsky performance status score of > 60 Exclusion criteria: Women who had received surgery or previous RT for cervical cancer were excluded; patients with other comorbidities and pregnant patients were excluded Gender: Female Type of cancer: Cervix Primary RT/adjuvant RT/other: Primary Other treatment received: All participants received concurrent weekly platinum-based chemotherapy (cisplatin 40 mg/m^2) and VBT(21 Gy in 3 weekly fractions) after EBRT
Interventions	Comparison: IMRT vs 3DCRT Arm 1: IMRT: 50 Gy/25 fractions delivered over 5 weeks. Dose constraints as follows: PTV D95 > 97%, bowel V45 ≤195 cc, rectum V40 ≤60%; femoral heads Dmax ≤ 50 Gy; bladder V45 ≤ 35%. Plan optimisation done using a dose-volume optimiser Arm 2: 3DCRT: 50 Gy/25 fractions delivered over 5 week; 4-field technique with collimator leaves conforming to PTV with 0.8cm margin Supine position on pelvic base plate. CT simulation was performed. Target volumes and OAR were delineated using RTOG guidelines by the same radiologist to avoid interpersonal differences. Generous margins given to PTV (1 - 1.5 cm) to account for uterine motion
Outcomes	GI Toxicity: Acute (CTCAE v4) QoL: NR Other review outcomes: Diarrhoea Other study outcomes: Dosimetric parameters, treatment delays Duration of follow-up: 90 days
Notes	Baseline characteristics were similar. Mean conformity index was reported as better with IMRT. Bowel V45 was less with IMRT. Acute GU toxicity grade ≥ 2 was reported as significantly reduced in the IMRT arm. Treatment was delayed for 4 women in the 3DCRT group and 1 woman in the IMRT group due to grade 3 diarrhoea

Naik 2016 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not clearly described - just states that "all patients were randomized into the two arms"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open" RCT
Blinding of outcome assessment	Unclear risk	Breaking the randomisation code and outcome assessor blinding is not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent missing data
Selective reporting (reporting bias)	Low risk	Most expected outcomes reported but protocol not seen
Other bias	Unclear risk	Unclear funding source
Overall judgement	Unclear risk	Insufficient methodological details

Nascimento 2014

Methods	Design: Randomised, double-blind, placebo-controlled pilot Trial Country: Brazil Accrual dates: February 2012 to October 2012 Trial Reg.: NCT 01901042 Funding source: NR
Participants	No. randomised: 21 Inclusion criteria: All patients referred for treatment of prostate cancer using 3DCRT from February 2012 to October 2012 Exclusion criteria: History of previous surgery involving the rectum, noncompliance with the intervention, and diagnosis of previous inflammatory bowel disease Gender: Male Age: Intervention: 64.3 (mean) 7.5 SD, Control: 70.4 (mean) 8.3 SD Type of cancer: Prostate Radiotherapy regimen received: 66 Gy - 76 Gy in standard fractionation Primary/adjuvant/other: Primary Other treatment received: NR

Interventions	Comparison: Synbiotic vs placebo Arm 1: Sachets (5 g) containing a synbiotic product in powder form with 4.3 g of dietary fibre (inulin plus partially hydrolysed guar gum mixture) and Lactobacillus reuteri in a concentration > 10(8) CFU/g (Nestle , Sao Paulo, Brazil) (synbiotic group). Treatment began 1 week before RT and continued for the next 4 weeks. All participants were instructed to dilute 1 sachet in a glass of water and drink once a day during the week before the beginning of RT sessions, increasing the dose to 2 sachets daily after the beginning of the sessions Arm 2: Identical-looking placebo
Outcomes	GI toxicity: NR QoL: EORTC QLQ-PRT23 Other review outcomes: NR Other study outcomes: NR Duration of follow-up: Until the 4th week of RT
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was done using a computerised random-number generator
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, radiographers and doctors were blinded to the intervention
Blinding of outcome assessment	Low risk	Participants, radiographers and doctors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the intevention and end point data
Selective reporting (reporting bias)	Unclear risk	We found no usable data for review outcomes
Other bias	Unclear risk	Pilot study with small sample size. Authors state that groups were homogeneous for age, BMI and RT dose and irradiated rectal volume. However, a power calculation is given based on a median 4-point difference in QLQ-PRT23 scores between groups of 4 points (max - min score: 84 - 21). Whilst the difference sought was based on a pre-

Nascimento 2014 (*Continued*)

		vious pilot study, it is not clear if this difference is clinically significant, but seems small given the possible 63 point difference in scores. Lower scores indicate fewer symptoms
Overall judgement	Unclear risk	Based on methodological concerns above

Nout 2009

Methods	Design: Multicentre, open-label, non-inferiority RCT Country: The Netherlands Trial Reg.: ISRCTN16228756 Accrual dates: May 2002 to Sept 2006 Funding source: Dutch Cancer Society grant (CKTO 2001-04)
Participants	No. randomised: 427 Inclusion criteria: Women with stage I or IIa endometrial adenocarcinoma with high-intermediate features namely, 1) age > 60 years and stage Ic grade 1 or 2 disease, or stage 1B grade 3 disease; and (2) stage IIa disease, any age (apart from grade 3 with > 50% myometrial invasion); Karnofsky performance score 0 - 2; written informed consent Exclusion criteria: serous or clear cell cancer, staging lymphadenectomy; interval between surgery and RT > 8 weeks; previous cancer; pprevious RT, hormonal therapy or chemotherapy; previous diagnosis of inflammatory bowel disease Gender: Female Type of cancer: Endometrial Primary RT/adjuvant RT/other: Adjuvant Other treatment received: Primary surgery consisted of TAH, BSO, node sampling of suspicious nodes, and peritoneal washings. Routine lymphadenectomy was not performed
Interventions	Comparison: BT vs EBRT Arm 1: BT: HDR BT 21 Gy in 3 fractions of 7 Gy over 2 weeks (90% of participants) or LDR BT 30 Gy in 1 fraction Arm 2: EBRT: 46 Gy in 23 fractions, 5 fractions a week Paticipants were asked to have a full bladder and empty rectum at the time of the CT scan and during treatment
Outcomes	GI toxicity: Acute and late (EORTC-RTOG) QoL: EORTC QLQ-PR25 Other review outcomes: NR Other study outcomes: Survival Duration of follow-up: 2 - 4 weeks after RT, then at 6, 12, 18, 24, 36, 48, and 60 months. QoL outcomes also reported at 7 and 10 years
Notes	Baseline characteristics were comparable, including performance score, age, comorbidity, FIGO stage, grade, and other factors reported. Mean duration of EBRT was 30.9 days vs 12.9 days in the BT group. "Longitudinal HRQL analysis showed persisting higher rates of bowel symptoms with EBRT…At 7 years, clinically relevant fecal leakage was

	reported by 10.6% in the EBRT group, versus 1.8% for VBT (P= .03), diarrhoea by 8.4% versus 0.9% (P=.04), limitations due to bowel symptoms by 10.5% versus 1.8% (P=.001), and bowel urgency by 23.3% versus 6.6% (P<.001)." This occurred without significant differences in overall QoL. (De Boer 2015)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated, biased coin minimisation"
Allocation concealment (selection bias)	Low risk	Assigned by Internet with an application trial online process (TOP). Stratified by stage, centre, brachytherapy (low-dose vs high-dose) and participant age
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open-label"
Blinding of outcome assessment	Low risk	"All investigators were masked to the assignment of treatment group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	23 protocol violations occurred and 11 participants who did not receive the allocated treatment. Relatively low attrition with 81% of participants responding to QoL surveys but consistently fewer responders in the EBRT group over time, which may have underestimated effects for this group
Selective reporting (reporting bias)	Low risk	All expected and prespecified outcomes were reported. Primary analyses were by ITT. Analysis of toxicity was based on treatment received
Other bias	Low risk	None noted
Overall judgement	Low risk	Good-quality RCT

O'Brien 1997

Methods	Design: Phase III RCT with double-blinding and stratification for institution Country: USA Accrual dates: May 1995 and Feb 1996 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 86 Inclusion criteria: Localised carcinoma of the prostate Exclusion criteria: In no case was the treatment designed to include the pelvic lymphatics Gender: Male Age: NR Type of cancer: Localised carcinoma of the prostate Radiotherapy regimen received: 3 of the 4 centres treated participants with total doses of 63 - 65 Gy at 2 Gy/fraction; the remaining centre treated 23 participants using a hypofractionated regimen of 52.5 Gy in 20 fractions Primary/adjuvant/other: Primary Other treatment received: None
Interventions	Comparison: Sucralfate vs placebo Arm 1: 3 g of sucralfate (15 mL suspension as a daily enema); the enema was begun on the first day of RT and continued until 2 weeks after treatment completion. The nursing staff administered the enema on the weekdays and the participant self-administered the enema on the weekends Arm 2: 15 mL suspension as a daily enema on its own; the enema was begun on the first day of RT and continued until 2 weeks after treatment completion. The nursing staff administered the enema on the weekdays and the participant self-administered the enema on the weekends
Outcomes	GI toxicity: Acute RTOG/EORTC QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: Median follow-up of 63 months
Notes	Overall 8 patients died, 5 in the placebo and 3 in the sucralfate arm; Kaplan-Meier risk of RTOG Grade 2 at 5 yrs, risk of rectal bleeding at year 5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Double blind RCT with a "block size of four and stratification by institution"
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind" with identical placebo

O'Brien 1997 (*Continued*)

Blinding of outcome assessment	Low risk	'Double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition (< 20%)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen but several review outcomes reported
Other bias	Unclear risk	Due to lack of baseline characteristics
Overall judgement	Low risk	Insufficient detail to make a judgement

Pal 2013

Methods	Design: RCT Country: India Accrual dates: November 2011 to July 2012 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 98 Inclusion criteria: Aged 18 - 70 yrs and meeting following criteria: attending the Outpatient Department with histologically-proven squamous cell carcinoma (SCC) of cervix; Karnofsky performance status (KPS) > 60; normal haematological, renal, and hepatic function Exclusion criteria: Pregnancy and lactation; history of prior chemotherapy or RT to the pelvic region, uncontrolled comorbid conditions, and with evidence of distant metastasis Gender: Female Age mean (range): Intervention: 56 (33 - 70), Control: 57 (35 - 70) Type of cancer: Locoregionally-advanced carcinoma of cervix Radiotherapy regimen received: 50 Gy in conventional fractionation; concurrent chemoratiation was followed by brachytherapy after a gap of 2 weeks Primary/adjuvant/other: Primary Other treatment received: Injections of cisplatin at the dose of 40 mg/m^2 of body surface area every week during RT for 5 wks
Interventions	Comparison: Sulfasalazine vs placebo Arm 1: Sulfasalazine 1000 mg orally x twice daily from the day of starting RT to 1 week after completion of treatment Arm 2: Placebo
Outcomes	GI toxicity: Acute CTC v4.0 QoL: (scale used) NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: From the start of the treatment to 4 weeks after chemoradiation
Notes	None

Pal 2013 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Pettersson 2012

Methods	Design: Randomised controlled trial Country: Sweden Accrual dates: January 2006 to January 2008 Trial Reg.: NR Funding source: This work was supported by the Cancer and Traffic Injury Fund, the Research Foundation of the Department of Oncology at Uppsala University, the Swedish Cancer Society, Uppsala County Council and Uppsala University
Participants	No. randomised: 130 Inclusion criteria: Patients referred to local curative RT with external beam radiotherapy (EBRT), in combination with either high-dose- rate brachytherapy or proton therapy Exclusion criteria: Previous radiotherapy to the pelvic/bowel area, diagnosis of inflammatory bowel disease, cognitive function impairment, long-term hospitalisation and inability to speak or understand Swedish Gender: Male Age median (range): Intervention: 67 (50 - 77), Control: 65 (54 - 76) Type of cancer: Prostate Radiotherapy regimen received: 70 Gy (brachytherapy 10 Gy/fraction up to 20 Gy, or proton therapy 5 Gy/fraction up to 20 Gy, in combination with EBRT 2 Gy/fraction up to 50 Gy) Primary/adjuvant/other: Primary Other treatment received: NR

Pettersson 2012 (*Continued*)

Interventions	Comparison: Dietary intervention vs control Arm 1: Advised to avoid foods high in insoluble dietary fibre and lactose and to instead consume foods with a higher proportion of soluble fibres and low in lactose during the entire study period (from baseline up to 24 months after end of RT). The dietary advice was standardised, with distinctions made between foods that should be eaten and foods to avoid. The participants received standardised dietary advice from a research dietitian in face-to-face sessions at baseline assessment and 4 weeks, through a phone call at 8 weeks as well as in a study-specific brochure at all assessments (baseline, 4 weeks, 8 weeks, 2 months after RT Arm 2: Advised to continue with their normal diet
Outcomes	GI toxicity: Acute and late EORTC QLQ-C30 (version 3) and QLQ-PR25 QoL: EORTC QLQ-C30 and QLQ-PR25 used but scores not reported by group Other review outcomes: NR Other study outcomes: NR Duration of follow-up: 26 months
Notes	In the 2012 article, 25% of participants in the Control group reported acute GI symptoms versus 10% in the intervention group, which may have affected longer-term outcomes. Other risk factors (smoking, diabetes, age) were reasonably distributed between intervention and control groups Symptoms were evaluated using specific aspects of different scales. For the purpose of review meta-analysis, we used the QLQ-C30 scores

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Method used was Efron's biased coin design
Allocation concealment (selection bias)	Low risk	Randomisation group only provided to patients after baseline (T0) assessment had been completed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Intervention unblinded to participants and investigators
Blinding of outcome assessment	High risk	Intervention unblinded to analysts
Incomplete outcome data (attrition bias) All outcomes	Low risk	Rates of attrition < 20% at all time points except for 24 months as follows: During RT: 15% (111/130); 3m post-RT: 13% (113/130); 12m post-RT: 18% (106/130) ; 24m post-RT: 22% (102/130)

Pettersson 2012 (*Continued*)

Selective reporting (reporting bias)	Low risk	All prespecified outcomes appear to have been reported
Other bias	Unclear risk	Toxicity rates (severity and incidence) were less than those predicted in statistically powering the trial and thus the trial may have been underpowered to detect a difference
Overall judgement	Unclear risk	No specific targets were set for the reduction of insoluble fibre or lactose intake, thus difficult to judge whether changes made by participants would have had a physiological effect. Unclear what possible impact underpowering of the trial may have had

Prada 2009

Methods	Design: Multicentre RCT Country: USA Accrual dates: January 2005 to July 2006 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 69 Inclusion criteria: Low- and intermediate-risk prostate cancer tumour Exclusion criteria: NR Gender: Male Age median: Arm 1 68 and Arm 2 69 years Type of cancer: Prostate Radiotherapy regimen received: Brachtherapy with implanted I-125 seeds; prescription dose of 145 Gy to the isodose Primary/adjuvant/other: Primary (brachy) Other treatment received: 31 participants received hormone therapy
Interventions	Comparison: Transperineal injections vs no injection Arm 1: Transperineal injection of 6 - 8 ml of hyaluronic acid (HA) in the perirectal fat after the implantation of I-125 seeds Arm 2: No transperineal HA injection
Outcomes	GI toxicity: Rectal bleeding (CTCAE v2) QoL: NR Other review outcomes: NR Other study outcomes: Mucosal cell damage on proctoscopic examination using a descriptive grading system (Grade 0 to 4) where 4 is life-threatening effects, such as obstruction, perforation and fistula Duration of follow-up: Median time to endoscopy was 26 months (range 21 to 39)

Notes	Baseline characteristics, including age, stage, Gleason score and hormone therapy were similar between study arms; however, a greater proportion of the HA group were low risk compared with the control group, which had more participants with intermediate risk prognostic factors Authors reported that "patients treated with brachytherapy I-125 and rectal protection with HA had significantly smaller incidence of mucosal damage at the proctoscopic examinations (5% vs. 36%, p=0.002)....than those treated with brachytherapy I-125 alone without HA. No toxicity was produced from the HA or its injection."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement; "patients were enrolled in a randomized clinical trial"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement; "patients were enrolled in a randomized clinical trial"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement but probably unblinded due to the nature of the intervention
Blinding of outcome assessment	Low risk	"The endoscopist was blinded to the treatment arm."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	High risk	Insufficient detail. No sample size calculation provided and it is unclear whether 69 participants are all those randomised, as loss to follow-up was not described; timing of follow-up and outcome assessment was not described; limited adverse event/toxicity reporting. Text refers to HA as "rectal protection", which suggests author bias
Other bias	Unclear risk	Control group comprised participants with slightly worse prognostic factors than the HA group; funding and conflicts of interest were not declared
Overall judgement	High risk	Due to apparent poor methodology described above

Ravasco 2005

Methods	Design: Prospective, randomised, controlled trial Country: Portugal Accrual dates: July 2000 to March 2003 Trial Reg.: NR Funding source: Supported by a grant from Nu cleo Regional do Sul da Liga Portuguesa contra o Cancro-Terry Fox Foundation
Participants	No. randomised: 111 Inclusion criteria: All consecutive CRC ambulatory patients referred for RT were considered eligible, regardless of whether the proposed RT was primary, adjuvant to surgery, combined with chemotherapy, or with palliative intent. Inclusion criteria were referral for RT treatment of 50.4 Gy administered in 28 fractions Exclusion criteria: Renal disease or diabetes mellitus or both Gender: 59.56% (2005); 48.54% (2012) male, 40.54% (2005); 41.46% (2012) female Age: Mean age of cohort was 58 ± 15 years (range: 32 - 88 years) Type of cancer: Colorectal cancer Radiotherapy regimen received: 50.4 Gy fractionated Primary/adjuvant/other: Primary Other treatment received: Preoperative RT combined with chemotherapy comprising fluorouracil plus folinic acid-based regimens administered concurrently with the first and the last 5 days of RT
Interventions	Comparison: Dietary counselling vs high-protein supplement vs regular diet Arm 1: Received individualised dietary counselling based on regular foods, taking account of need for adequate intake, digestive capacity, symptoms and psychological factors Arm 2: Were asked to consume 2 cans (20 g protein and 200 kcal) per day of a high-protein liquid supplement in addition to their usual diet Arm 3: The control group, participants were instructed to maintain their ad libitum intake
Outcomes	GI toxicity: Acute EORTC/RTOG QoL: EORTC QLQ-C30 Other review outcomes: NR Other study outcomes: QoL was assessed at the three time points, always using the EORTC Quality of Life Questionnaire version 3.0 (EORTC-QLQ C30). Nutritional status was assessed using PG-SGA and BMI. Nutritional intake (energy and protein) was assessed using Diet History and 24-hour recall at each scheduled interview. Compliance Duration of follow-up: During RT and 3 months after RT (2005 article) median follow-up = 6.5 years (2012 article)
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients randomly assigned at enrolment in permutation blocks of 3, stratified by can-

Ravasco 2005 (*Continued*)

		cer stage
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes contained the computer-generated allocation assignments. The randomisation schedule was kept separately from study personnel. Randomisation envelopes were opened before the first appointment with the patient by a person blind to study procedures
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and study personnel were not blinded
Blinding of outcome assessment	High risk	Study investigators were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Between baseline and 3 months with all 111 participants completing all study assessments. At median follow-up 6.5 years with data available from 89 participants (20% attrition)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Nutritional intake, nutritional status, symptom-induced morbidity (anorexia, nausea and vomiting) did not differ between groups
Overall judgement	Low risk	

Razzaghdoust 2014

Methods	Design: Phase I/II randomised placebo-controlled trial Country: Iran Accrual dates: April 2012 to February 2013 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 36 Inclusion criteria: Localised adenocarcinoma of the prostate (stage T2b - T4) and were candidates for definitive or postoperative EBRT. These patients had to have normal renal and liver function, a haemoglobin level > 9 g/dl, WBC count > 2500/μl and a platelet count > 100,000/μl Exclusion criteria: Patients with metastatic prostate cancer; patients previously treated with RT or chemotherapy; patients with clinically-evident pulmonary insufficiency; patients with serum creatinine or liver enzyme serum levels > 1.5 and 2.5 times the normal values, respectively; patients receiving any H2-receptor antagonist simultaneously and

	patients with allergic reaction in consequence of famotidine administration Gender: Male Age mean (SD): Intervention: 67.8 (8.1), Control: 65.9 (8.1) Type of cancer: Prostate Radiotherapy regimen received: 66 Gy - 70 Gy standard fractionation Primary/adjuvant/other: Primary Other treatment received: None
Interventions	Comparison: Famotidine vs placebo Arm 1: 40 mg of oral famotidine, the first tablet was administered 4 hours prior to each RT fraction and the second tablet 3 hours before each fraction Arm 2: Placebo tablets twice daily (5 days/week); the first tablet was administered 4 hours prior to each RT fraction and the second tablet 3 hours before each fraction
Outcomes	GI toxicity: Acute toxicity (RTOG) QoL: NR Other review outcomes: NR Other study outcomes: Duration of rectal toxicity (≥ grade I), Duration of urinary toxicity (≥ grade I) Duration of follow-up: Unclear
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"For allocation of the participants, a computer-generated randomization list was drawn up by the statistician. An off-site person was employed for allocating either famotidine or placebo to group A or B. All patients, investigators and study-site personnel were blinded to group assignment."
Allocation concealment (selection bias)	Low risk	"For allocation of the participants, a computer-generated randomization list was drawn up by the statistician. An off-site person was employed for allocating either famotidine or placebo to group A or B. All patients, investigators and study-site personnel were blinded to group assignment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All patients, investigators and study-site personnel were blinded to group assignment." Placebo was used

Razzaghdoust 2014 (*Continued*)

Blinding of outcome assessment	Low risk	"All patients, investigators and study-site personnel were blinded to group assignment." Placebo was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Total of 2 patients in group B were excluded. The reasons for exclusions were side effect and withdrawal of consent, each occurring in one patient"
Selective reporting (reporting bias)	Low risk	Protocol not seen but expected acute outcomes were reported
Other bias	Unclear risk	Small pilot study
Overall judgement	Unclear risk	Based on above

Resbeut 1997

Methods	Design: RCT, double-blind placebo, multicentre Country: France Accrual dates: February 1993 and May 1994 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 153 Inclusion criteria: Aged > 18 and < 80 years, Karnofsky index ≥ 80 Exclusion criteria: Concomitant chemotherapy, past history of abdominal irradiation, intestinal resection or colostomy, hypersensitivity to salicylates, diarrhoea before the beginning of pelvic irradiation Gender: 64.4% male Age mean (SE): Intervention: 64 (9.5), Control: 62.8 (9.5) Type of cancer: Prostate or uterus cancer Radiotherapy regimen received: Whole pelvic external irradiation ≥ 45 Gy in 4.5 - 5 weeks; no participant received more than 52 Gy in the whole pelvis Primary/adjuvant/other: Primary Other treatment received: When diarrhoea occurred, treatments with loperamide or actapulgit
Interventions	Comparison: 5-ASA (mesalazine, pentasa 500 mg) vs placebo Arm 1: 5-ASA 4 g/day administered orally throughout the irradiation period, 2 tablets 4 times a day Arm 2: Placebo tablets (colouring agent, activated charcoal, magnesium stearate, talc, microcristalline cellulose and purified water)
Outcomes	GI toxicity: WHO classification QoL: (scale used) NR Other review outcomes: NR Other study outcomes: Duration of diarrhoea

Resbeut 1997 (*Continued*)

	Duration of follow-up: 3 months post-RT	
Notes	68.5% males in 5-ASA vs 60.3% in placebo; not statistically significant	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgment.
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgment.
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgment.
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgment.
Other bias	Unclear risk	Insufficient detail to make a judgment.
Overall judgement	Unclear risk	Insufficient detail to make a judgment.

Rotovnik Kozjek 2011

Methods	Design: Randomised double-blinded, placebo-controlled pilot study Country: Slovenia Accrual dates: May 2008 to ? Trial Reg.: NR Funding source: Extra costs for laboratory analysis and nutritional supplements were covered from Research programme P4-0092 Ministry of Science Republic of Slovenia; Glutamine powder was provided by Peeroton Warenhandelsgesellschaft m.b.H. (Austria) . Maltodextrin powder was provided by Nutricia, Cuijk (Netherlands)
Participants	No. randomised: 41 Inclusion criteria: Rectal cancer patients receiving preoperative radiochemotherapy Exclusion criteria: NR Gender: 58.5% male Age mean (SD): Intervention: 60.5 (14.2), Control: 63.6 (10.12) Type of cancer: Rectal cancer Radiotherapy regimen received: A total irradiation dose of 45 Gy was administered to the pelvis in 1.8 Gy daily fractions over 5 weeks and 5.4 Gy as a boost to the primary tumour

	Primary/adjuvant/other: Primary Other treatment received: Chemotherapy was administered concomitantly with radiotherapy and consisted of capecitabine given orally at a daily dose of 1650 mg/m^2, divided in 2 equal doses given 12 hours apart. 1 dose was taken 1 hour prior to irradiation. Chemotherapy started on the first day of RT and finished on the last day of RT (including weekends)
Interventions	Comparison: Glutamine vs placebo Arm 1: 30 g of glutamine orally in 3 doses a day at the start of radiochemotherapy and for the subsequent 5 weeks of standard preoperative treatment of rectal cancer with radiochemotherapy; Participants were asked to take the supplement before their meals Arm 2: 30 g of maltodextrin as placebo oral supplement, divided into 3 doses; Participants were asked to take the supplement before their meals
Outcomes	GI toxicity: Acute Nci criteria (diarrhoea) QoL: NR Other review outcomes: NR Other study outcomes: Hormonal and inflammatory response Duration of follow-up: 5 weeks during preoperative radiochemotherapy
Notes	T3N0: glutamine (30.8%) vs placebo (44.4%); Glutamine T2N0 7.7% & T4N0 7.7%; Placebo T2N2 5.6% & T4N2 5.6%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The closed envelopes were randomly allocated in a 1:1 ratio to control or glutamine group using computer generated randomisation"
Allocation concealment (selection bias)	Low risk	"The closed envelopes were randomly allocated in a 1:1 ratio to control or glutamine group using computer generated randomisation" "Computerized randomisation was made at department for clinical studies. Random numbers were allocated to sequentially numbered containers for glutamine and placebo."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study was double blinded for medical personal and patients. Pharmacist was the only person who knew which numbers were allocated to which treatment group."
Blinding of outcome assessment	Low risk	"The study was double blinded for medical personal and patients. Pharmacist was the only person who knew which numbers

		were allocated to which treatment group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Eight patients dropped out (4 glutamine, 4 placebo group). Both groups of patients were similar in age, weight and nutritional status"
Selective reporting (reporting bias)	Low risk	No concerns noted
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Low risk	Low risk overall

Salminen 1988

Methods	Design: Randomised controlled tTrial Country: Finland Accrual dates: NR Trial Reg.: NR Funding source: 6 weeks after RT
Participants	No. randomised: 24 Inclusion criteria: Patients suffering from gynaecological malignancies andn scheduled for internal and external irradiation of the pelvic area (pelvic dose 5000 cGy) Exclusion criteria: Diabetics and patients with gastrointestinal disorders Gender: Female Age: 40 - 75 Type of cancer: Cervix or uterus carcinoma. Radiotherapy regimen received: 4400 cGy in 22 fractions daily in a split course Primary/adjuvant/other: Primary and adjuvant Other treatment received: After an interval of 1 to 2 weeks a Wertheim hysterectomy was performed
Interventions	Comparison: Probiotic vs control Arm 1: Daily 150 ml of yoghurt-type product containing at least 2 x 10(9) live Lactobacillus acidophilus bacteria, starting 5 days prior to RT, daily throughout RT (including the interval for surgery) and then for 10 days after end of RT. Dietary advice emphasising sufficient energy and protein intake, and avoidance of certain foods to prevent gastrointestinal side effects Arm 2: Dietary advice only with emphasis on sufficient protein and energy intake, including small meals and low fibre, low lactose, low fat
Outcomes	GI toxicity: Acute Unvalidated Scale QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: 6 weeks after RT

Salminen 1988 (*Continued*)

Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/24 excluded from analysis
Selective reporting (reporting bias)	Unclear risk	The authors specified that they aimed to report on frequency and severity of side effects. However, validated scales were not used, participants were interviewed about their 'subjective' feelings and side effects
Other bias	High risk	Baseline values not fully reported. Small study not statistically powered. Study now nearly 30 years old, so RT techniques will have changed to conformal / IMRT
Overall judgement	High risk	Non-blinded study, possibly subject to investigator bias during interviews during which validated (standardised) tools were not used

Sanguineti 2003

Methods	Design: Randomised study Country: Italy ? Accrual dates: August 1999 to May 2001 ? Trial Reg.: NR Funding source: NR
Participants	No. randomised: 134 Inclusion criteria: Patients with localised prostate carcinoma (T1-4 N0-x M0) who were to receive 3DCRT to 76 Gy Exclusion criteria: NR

	Gender: Male Age: NR Type of cancer: Prostate carcinoma Radiotherapy regimen received: Participants were treated at 2 Gy per fraction, 5 fractions a week. The radiation dose was prescribed to the isocenter (ICRU point). When initially included in target, the seminal vesicles were excluded at 60 Gy; treatment was limited to the prostate or seminal vesicles or both Primary/adjuvant/other: Primary Other treatment received: Most of the participants (n = 96, 71.6%) were on some form of androgen ablation at the time of 3DCRT
Interventions	Comparison: Sucralfate vs mesalazine vs hydrocortisone Arm 1: Mesalazine (5-ASA) 4 g gel enema; the 2 other drugs had already been manufactured with special devices to allow the proper dose and administration in the lower rectum Arm 2: Hydrocortisone 100 mg foam enema; The 2 other drugs had already been manufactured with special devices to allow the proper dose and administration in the lower rectum
Outcomes	GI toxicity: NR RTOG criteria QoL: NR Other review outcomes: NR Other study outcomes: Time to occurrence of grade 2+ acute rectal toxicity Duration of follow-up: 10 weeks ?
Notes	After the first 24 participants had been treated, arm 2 was discontinued because out of 8 participants receiving mesalazine, 7 actually developed acute rectal toxicity; Most participants had short delays related to holidays or machine breakdown; longer treatment gaps were generally due to intercurrent illness or local urinary complications

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Low risk	"Patients were given a closed envelope with drug prescription and directions for intake on a self-administration basis."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Randomization was blind to the treating physician. However, due to the lack of financial support and drug company interest, masking to patient was not possible. In order to minimize the bias due to the lack of blinding, we decided to give a treatment to all arms. Topical sucralfate was chosen because it had not shown any benefit over

Sanguineti 2003 (*Continued*)

		placebo in a previous double- blind randomized study"
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	"The trial was opened in August 1999, and after the first 24 patients had been treated, arm 2 was discontinued because of eight patients receiving mesalazine, seven actually developed acute rectal toxicity (five patients grade 3 and two patients grade 2)"
Selective reporting (reporting bias)	High risk	"The trial was opened in August 1999, and after the first 24 patients had been treated, arm 2 was discontinued because of eight patients receiving mesalazine, seven actually developed acute rectal toxicity (five patients grade 3 and two patients grade 2)"
Other bias	High risk	Unplanned interim analysis led to discontinuation of mesalazine
Overall judgement	High risk	"The trial was opened in August 1999, and after the first 24 patients had been treated, arm 2 was discontinued because of eight patients receiving mesalazine, seven actually developed acute rectal toxicity (five patients grade 3 and two patients grade 2)"

Shukla 2010

Methods	Design: RCT Country: India Accrual dates: July 2006 to June 2008 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 252 (229 analysed) Inclusion criteria: histologically-confirmed nonmetastatic carcinoma of the cervix with Karnofsky performance status of 70% or above and stage IIB - IIIB Exclusion criteria: any intestinal pathology that might interfere with primary end point assessment and those who smoked during the treatment Gender: Female Age mean: Intervention about 49 years, Control about 50 years Type of cancer: Cervix Radiotherapy regimen received: All participants had external radiation to the whole pelvis using anterior and posterior parallel opposing fields to a dose of 50Gy in 25 fractions at 5 fractions/wk

	Primary/adjuvant/other: Primary Other treatment received: Intracavitary brachytherapy; participants were given symptomatic treatment such as antimotility drugs and intravenous fluids as and when required
Interventions	Comparison: Evening vs morning RT Arm 1: Evening RT (6pm to 8pm) Arm 2: Morning RT (8am to 10 am)
Outcomes	GI Toxicity: acute (RTOG) QoL: NR Other review outcomes: NR Other study outcomes: Tumour response, other toxicity Duration of follow-up: NR; weekly follow-up during treatment
Notes	Baseline characteristics were comparable between groups including age, tumour stage and grade, haemoglobin levels and Karnofsky performance status. The overall treatment time for Group A was 36.33 days and for Group B was 35.64 days. The overall radiotherapy-induced mucositis (grades I - IV) in participants of the 2 groups was found to be significantly higher in the morning arm (P < .01). Other radiation-induced toxicity was also higher in the morning arm, but its occurrence in the 2 arms did not differ significantly (13.45% vs 12.73%, P > .05) 23 participants were excluded after randomisation: 8 due to non-treatment-related reasons and 15 due to non-mucositis-related reasons, such as leucopenia (haematological complications). Judging from the numbers in each group, more participants in the evening group were excluded than in the morning group, which could have biased the results (particularly those on haematological toxicity) We tried to contact the authors for clarification of reasons for withdrawal in each group but were unsuccessful

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated, but interventions cannot be blinded
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Out of 23 excluded patients, 8 did not complete treatment because of reasons other than treatment-related problems, and 15 had radiation interrupted during the treatment because of complications developed

Shukla 2010 (*Continued*)

		other than mucositis. Judging from the numbers in each group, more participants in the evening group were excluded than in the morning group. This could have biased the results
Selective reporting (reporting bias)	Low risk	Protocol not seen, but methods and expected outcomes were clearly reported
Other bias	Low risk	None noted; baseline characteristics were similar
Overall judgement	High risk	Significant methodological limitations introduced by post-randomisation exclusions

Sidik 2007

Methods	Design: Open parallel-arm RCT Country: Indonesia Accrual dates: July 2004 to January 2006 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 65 Inclusion criteria: Patients with cervix cancer stage I to IIIb who had received pelvic RT according to the Department protocol Exclusion criteria: Pneumothorax, metabolic disease, diabetes mellitus, malnutrition, other chronic diseases, depression and not willing to join the study Gender: Female Age mean: Intervention 47, Control 44 Type of cancer: Cervix Radiotherapy regimen received: NR Primary/adjuvant/other: NR Other treatment received: NR
Interventions	Comparison: HBOT vs no HBOT Arm 1: HBO after receiving RT. 100% oxygen (O_2) with pressure between 2 - 3 atmosphere absolute (ATA) in High Pressure Chamber (HPC) Arm 2: No HBOT
Outcomes	GI toxicity: Acute and late (LENT-SOMA) QoL: Karnofsky score Other review outcomes: NR Duration of follow-up: 6 months. Appeared to be an early measurement after RT and 1 at 6 months
Notes	Details of the timing and frequency of this intervention were sparse; however, from the report it seems that HBO was administered to women who had completed their course of pelvic RT. "Among 32 patients receiving HBOT, most of them received HBOT for

	more than 18 times". Baseline characteristics, namely age, weight, height, and blood parameters were comparable between study arms. However, scant outcome data were reported with change in quality of life reported as a percentage change and standard deviation. "Quality of life was measured with Karnofsky score and ratio of side effect using the LENT SOMA scale" and it was unclear how the presented data scores were calculated in Table 5. Authors reported in conclusion that "The HBOT procedure yield hyperoxia, hypervascular and hypercellular that improved the tissue damage after pelvic radiation. This condition will decrease acute and late side effect showed by LENT SOMA scale and improved quality of life shown by Karnofsky score."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insuficient detail. " block randomization was performed"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open RCT
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	28% attrition for 6 month follow-up data
Selective reporting (reporting bias)	Unclear risk	Unusual reporting of results with ratio of side effects and QoL reported as percentages with standard deviations. These data could not be used for review meta-analyses. Large effect difference with such a small sample size suggests the possibility of reporting bias
Other bias	Unclear risk	The intervention (HBOT) and RT treatment is not clearly described
Overall judgement	High risk	Serious study design limitations

Stellermans 2002

Methods	Design: Double-blind placebo-controlled randomised study Country: Belgium ? Accrual dates: January 1994 to September 1998 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 108 Inclusion criteria: Anatomopathologically-proven diagnosis of a malignancy of the rectum, the cervix or the corpus uteri, and an ECOG performance status of 0 - 2 Exclusion criteria: Patients who had undergone previous pelvic RT, who had pre-exisitng gastrointestinal problems or were diabetic Gender: NR Age: NR Type of cancer: Malignancy of the rectum (53/80), cervix (13/80) or endometrium (14/80) Radiotherapy regimen received: 45 Gy - 66 Gy in standard fractionation Primary/adjuvant/other: Primary Other treatment received: Most of the participants with rectal carcinoma received concomitant chemotherapy
Interventions	Comparison: sulcrafate vs placebo Arm 1: Sulcrafate was prepared as an oral suspension. Patients took medication 4 times a day (2 g at 08:00 and 20:00 hour, and 1 g at 12:00 and 16:00 hours) from start to end of RT, weekends included Arm 2: Identical placebo
Outcomes	GI toxicity: Acute Unvalidated (diarrhoea scores only) QoL: (scale used) Other review outcomes: Other study outcomes: Duration of follow-up: 6 weeks
Notes	Diarrhoea scores reported graphically - showed no statistically significant difference between the arms

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was "identical in taste and consistency"

Stellermans 2002 (*Continued*)

Blinding of outcome assessment	Low risk	Placebo was "identical in taste and consistency"
Incomplete outcome data (attrition bias) All outcomes	High risk	80/108 patients were evaluated - post-randomisation attrition/withdrawal rate was greater than 20%. 8 withdrew because of bad tolerance to the medication (5 in sucralfate and 3 in placebo group); 17 participants were "unevaluable due to insufficient information"; 3 did not start RT
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Low risk	"Of these 80 patients, 38 were in the sucralfate group and 42 in the placebo group. The patients were well balanced between the two groups. (Table 1)."
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Stryker 1979

Methods	Design: Randomised Country: USA Accrual dates: NR Trial Reg.: NR Funding source: NR
Participants	No. randomised: 35 (32 analysed) Inclusion criteria: Patients scheduled to begin pelvic irradiation for malignant disease Exclusion criteria: NR Gender: 96.9% female Age: Intervention: 60 ± 3 years (41 - 76), Control: 56 ± 3 years (34 - 77) Type of cancer: Gynaecological (31/32), prostate (1/32) Radiotherapy regimen received: 850 to 900 rad per week fractionated over 5 to 6 weeks Primary/adjuvant/other: Primary Other treatment received: Ibuprofen participants received diphenoxylate hydrocloride with atropine sulfate on request if they reported 4 or more stools/day. Prochlorperazine for nausea
Interventions	Comparison: Ibuprofen vs control Arm 1: 400 mg ibuprofen orally four times/day Arm 2: prochlorperazine 10 mg three times a day. for nausea, or diphenoxylate with atropine sulfate 2.5 mg four times a day when requested
Outcomes	GI toxicity: Acute, Unvalidated scale QoL: (scale used) NR Other review outcomes: NR

Stryker 1979 (*Continued*)

	Other study outcomes: NR Duration of follow-up: During RT
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Stryker 1983

Methods	Design: Randomised Country: USA Accrual dates: NR Trial Reg.: NR Funding source: Colestipol hydrochloride (trademark-colostid) supplied by Mr Edward Gorrell, Medical Sciences liaison representative, The Ujohn Company
Participants	No. randomised: 33 (31 analysed) Inclusion criteria: Patients undergoing pelvic RT Exclusion criteria: NR Gender: 12.9% male Age mean (range): Intervention: 60.5 (44 - 72), Control: 53.1 (25 - 76) Type of cancer: Bladder (2/31), cervix (11/31), endometrium (13/31), prostate (2/31), vagina (2/31), rectum (1/31) Radiotherapy regimen received: 3420 rad to 5100 rad fractionated Primary/adjuvant/other: Primary and adjuvant Other treatment received: A number of participants in each group had additional RT

Stryker 1983 (*Continued*)

	boosts
Interventions	Comparison: Colestipol hydrochloride vs control Arm 1: Prophylactic colestipol hydrochloride 5 grams 4 times a day mixed with water or other fluids such as fruit juice during entire time of RT Arm 2: RT alone. diphenoxylate hydrochloride and atropine sulfate 2.5 - 20 mg a day as requested if they experienced diarrhoea
Outcomes	GI toxicity: ? Ungraded QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT
Notes	Age range was not comparable between groups, 8 participants in the intervention group discontinued drug

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control was RT alone, no placebo
Blinding of outcome assessment	High risk	Control was RT alone, no placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	Control was RT alone, no placebo
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Low risk	None noted
Overall judgement	Unclear risk	Based on methodological uncertainties above

Stryker 1986

Methods	Design: 3-arm, randomised controlled trial Country: USA Accrual dates: NR Trial Reg.: NR Funding source: The lactose was hydrolysed by lactase enzyme kindly supplied by Alan E. Kligerman, SugarLo Company, Atlantic City, NJ
Participants	No. randomised: 64 (53 analysed) Inclusion criteria: Patients due to undergo pelvic RT for a malignant neoplasm. None of the patients gave a history of nil intolerance or chronic gastrointestinal disease Exclusion criteria: NR Gender: 89% male Age: Intervention 1: 61, Intervention 2: 58, Control: 57 Type of cancer: Endometrium (29/53), cervix (15/53), Vagina (4/53), Prostate (3/53), ovary (1/53), sigmoid colon (1/53) Radiotherapy regimen received: 170 rad or 180 rad 5 daily for 5 consecutive weeks Primary/adjuvant/other: Primary Other treatment received: NR
Interventions	Comparison: Lactose-restricted diet vs modified lactose vs regular diet Arm 1: Lactose-restricted diet during RT. Instructed to take calcium tablets 625 mg 3 times daily to compensate for reduced calcium intake Arm 2: Diet of 480 cc of milk a day with 90% of the lactose hydrolysed to glucose and galactose Arm 3: Regular diet , instucted to drink at least 480 cc of milk daily
Outcomes	GI toxicity: Participant assessed daily stool frequency and (anti-diarrhoeal) medication days QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT (5 weeks)
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated, suspect unblinded to participants and investigator
Blinding of outcome assessment	High risk	Not stated, suspect unblinded

Stryker 1986 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Study may have been underpowered, no power statement provided. Overall, 18% excluded as they failed to complete the 4-week intervention with most dropouts in the control (3/21) and Int 2 (6/22) groups
Selective reporting (reporting bias)	High risk	Stated outcomes provided but no primary outcome prespecified and no power calculation given
Other bias	Unclear risk	Insufficient detail to make a judgement.
Overall judgement	High risk	

Tait 1997

Methods	Design: Open-label parallel-arm RCT Country: UK Trial Reg.: NR Accrual dates: 1988 and 1993 Funding source: Cancer Research Campaign programme grant, the Bob Champion Cancer Trust, and the NHS Executive
Participants	No. randomised: 274 (266 analysed) Inclusion criteria: Patients undergoing CT planning for pelvic radiotherapy comprising 4 or fewer fields were eligible to include either radical or high-dose palliative treatments Exclusion criteria: 'Prior cytotoxic chemotherapy and hormone manipulation were not exclusion criteria." Gender: 85% male Type of cancer: Mainly prostate (52%), bladder (41%) and rectum (5%) Primary RT/adjuvant RT/other: Primary Other treatment received: NR
Interventions	Comparison: 3DCRT vs conventional RT Arm 1: 3DCRT: Total dose of 60 - 64 GY in 2 Gy fractions 5 times a week. Used customised cerrobend blocks to shape the radiation beams with a 6 mm margin around the beam's eye-view projection of the PTV Arm 2: ConRT: Total dose of 60 - 64 GY in 2 Gy fractions 5 times a week with standard rectangular radiation field Delivered in a 3-field technique. 56 participants were treated with 6 Gy fractions once a week for 5 or 6 weeks and 38 participants were treated with an accelerated fractionation regimen of 1.8 or 2 Gy fractions twice a day in 32 fractions over 4 weeks. Participants receiving these varied regimens were balanced across treatment arms
Outcomes	GI toxicity: Acute (EORTC-RTOG and participant-reported questionnaire "based on EORTC-RTOG", with symptoms coded 1 to 4 with increasing severity) QoL: NR Other review outcomes: Medication for syptom relief

Tait 1997 (*Continued*)

	Other study outcomes: Fatigue, nausea/vomiting and bladder problem scores Duration of follow-up: Weekly during and for 3 weeks after treatment, then monthly for a further 2 months
Notes	Baseline characteristics (age, gender, tumour site, fractionation scheme, weight, dose and anterior field volume) were comparable. However, the proportion of participants undergoing chemotherapy or hormone therapy in each arm was not stated. Median dose-volume for 3DCRT and conRT were 689 cm^3 and 792 cm^3, respectively - a 13% difference (P = 0.02), based on 74 consecutive participants. Authors reported no statistically significant difference in acute toxicity but no usable data could be extracted for meta-analysis. Also reported the mean number of bowel motions on and off treatment, which were similar between the 3DCRT and conRT groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomised permuted blocks design from an independent randomisation service offered by the Clinical Trials and Statistics Unit, Institute of Cancer Research"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	"unblinded"
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 patients were excluded post-randomisation due to medical unsuitability, administrative errors and loss to follow-up; 5 participants did not complete questionnaires; in general, good compliance
Selective reporting (reporting bias)	Unclear risk	Late toxicity was not reported and baseline characteristics were scanty
Other bias	Low risk	None noted
Overall judgement	Unclear risk	Due to scanty methodological details and inadequate reporting

Timko 2010

Methods	Design: Randomised parallel-group non-placebo-controlled trial Country: Slovakia Accrual dates: June 2005 to March 2006 Trial Reg.: NR Funding source: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors
Participants	No. randomised: 42 Inclusion criteria: Oncology patients who underwent adjuvant postoperative RT in the abdominal and pelvic region. Patients who received RT with CHT were also included. No gastrointestinal disorders Exclusion criteria: Previous radiation treatments, current antibiotics therapy, the use of antibiotics during the previous 2 weeks, established gastrointestinal disease (chronic diarrhoea, Crohn's disease, ulcerative colitis). Any patient whose medical condition required antibiotic therapy during RT was excluded from the group Gender: 66.67% male Age (range): Intervention: 62 (34 - 82), Control: 67 (43 - 83) Type of cancer: Colorectal (13/42), rectosigmoid junction (10/42), uterine (4/42), urinary bladder (4/42), cervical (1/42), sigmoid (1/42), anus and anal canal tumour (1/42) , prostate (8/42) Radiotherapy regimen received: 50 Gy to 67 Gy in standard fractionation Primary/adjuvant/other: Adjuvant Other treatment received: Patients who received CT/RT were included: 55% of participants in Int 1 (Dophilus) and 50% in Control (Hylak) received concommitant CT (500 mg 5-FU)
Interventions	Comparison: Probiotic vs synbiotic Arm 1: Study participants in L-Group received the probiotic preparation "5" Strain Dophilus with an enteric coating and containing 5 probiotic cultures (55% Lactobacillus rhamnosus, 20% Bifidobacterium adolescentis, 5% L. acidophilus, 5% Bifidobacterium longum, 15% Enterococcus faecium) with a count of 6 billion active bacteria/capsule at a daily dosage of 2 capsules Arm 2: Participants in H-Group received the Hylak Tropfen Forte preparation, i.e. cell-free fermentation products of Lactobacillus helveticus and gut symbionts (100 ml 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 40 drops, three times a day
Outcomes	GI toxicity: Acute (unvalidated participant-assessed scale) QoL: Unvalidated participant assessed Other review outcomes: NR Other study outcomes: NR Duration of follow-up: During RT
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement

Timko 2010 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Presumed unblinded to participants and investigators. Investigators who gave 2 different preparations. Authors do not state that the trial was blinded
Blinding of outcome assessment	High risk	Presumed unblinded to assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the intervention
Selective reporting (reporting bias)	Low risk	All stated aims reported
Other bias	High risk	Baseline values not reported. Small study, not statistically powered. Authors state that study groups were not balanced for gender and primary tumour site. No information on method of instructing participants to keep symptom/bowel diaries. Non-validated scales used
Overall judgement	High risk	High risk overall.

Valls 1991

Methods	Design: Randomised double-blind trial Country: Spain Accrual dates: May 1989 to April 1990 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 38 Inclusion criteria: Between 20 and 80 years old, without diarrhoea and with a Karnofsky index > 60%, undergoing whole pelvic irradiation Exclusion criteria: Those who suffered diarrhoea before starting treatment with Karnofsky index < 60%. Those who did not give consent once informed on their condition and the nature of the trial. Those who because of their anatomy or extension of their tumour, the habitual technique did not apply Gender: 53% male Age: NR Type of cancer: Mixed pelvic Radiotherapy regimen received: 46 Gy in standard fractionation Primary/adjuvant/other: PR and POR Other treatment received: Surgery, colostomy and chemotherapy

Valls 1991 (*Continued*)

Interventions	Comparison: Sulcrafate vs placebo Arm 1: Sucralfate (1 g/6 hours) oral during the treatment period and for 3 weeks after RT Arm 2: Placebo (lactose) (1 g/6 hours) during the treatment period and for 3 weeks after RT
Outcomes	GI toxicity: Unvalidated investigators' scale. QoL: (scale used):NR Other review outcomes: NR Other study outcomes: Secondary outcomes reported were; anorexia (sucralfate 4, placebo 6), borborygm (sucralfate 10, placebo 12), colic pain (sucralfate 7, placebo 9) Duration of follow-up: 3 weeks post-RT
Notes	10 participants had a colostomy. Baseline characteristics were comparable between groups including age, surgery, chemotherapy and type of cancer. Patrticipats in the placebo group passed more stools then tthe sucralphate group on avarage per week. P = 0.06

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random-number table
Allocation concealment (selection bias)	Low risk	Allocation performed by pharmacy staff at point of medication collection
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment	Low risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants included in the trial, in different phases of treatment, were not considered
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	High risk	7 in the intervention arm and 3 in the placebo arm had colostomies. Baseline imbalance in number of weekly stools. Placebo group had average of 18 stools and sucralfate group 13 at start of treatment. Problematic definition and graduation of diuretic syndrome
Overall judgement	High risk	For reason above

Valls 1999

Methods	Design: Multicentric double-blind randomised clinical trial Country: Spain Accrual dates: NR Trial Reg.: NR Funding source: NR
Participants	No. randomised: 120 Inclusion criteria: With a localised pelvic cancer, 18 to 80 years old, with a Karnofsky index of 80% or more, and "normal" defaecation habits (3 - 10 daefecations/week), undergoing whole pelvic irradiation, were included Exclusion criteria: Patients affected by metastatic disease; gastrointestinal disorders or did not have a normal (3 - 10 stools a week) stool rhythm; antineoplastic chemotherapy or any other substance that could act as a radiosensitive agent, previous abdominal or lumbosacral spine RT; abdominal cavity surgery (opening of the peritoneum); peritoneal adhesions; those who by their IQ, life style or who voluntarily were not able to follow test conditions; those who did not, in general, meet the conditions of the study or did not give their consent in writing Gender: 20% male Age: NR Type of cancer: Endometrial, cervical, vaginal, prostate Radiotherapy regimen received: 45 - 50 Gy in standard fractionation Primary/adjuvant/other: PR Other treatment received: NR
Interventions	Comparison: Sulcrafate vs placebo Arm 1: The first week all participants received placebo. In the second week the participants were randomised into 2 groups: sucralfate (61 participants, 2 g orally three times a day. before meals) and placebo (59 participants). RT started at the beginning of the third week and lasted until the end of the study (7 weeks) Arm 2: As above
Outcomes	GI toxicity: NR QoL: NR Other review outcomes: NR Other study outcomes: NR Duration of follow-up: 7 weeks
Notes	This study assessed GI toxicity by the average number of daily stools (sucralfate group = 1.48, placebo group = 1.53) and weekly capsules of loperamide (sucralfate group = 154, placebo group = 286). Analysis of the variance of the percentage of formed faeces for each group over the treatment period is significant (P < 0.05) (sucralfate group = 65.6, placebo group = 51.1) The study showed that the comsumption of loperamide was significantly lower in the sucralfate group (P < 0.001)

Risk of bias

Bias	Authors' judgement	Support for judgement

Valls 1999 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computerised random protocol number
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	"20 participants did not meet all the requirements until the end of the seventh week, and were excluded. Any serious side effects attributable to the medication or manifest inefficiency of any of the treatments led to exclusion from the study. In these cases, the investigator took the therapeutic measures considered most appropriate. Cases in which the baseline disease reaction was non controllable with supplementary measures (diet, loperamide), leading to a recommended change in treatment strategy, were excluded from the trial"
Selective reporting (reporting bias)	Unclear risk	Data were not reported in a usable form for this review
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Insufficient detail to make a judgement

Van Lin 2007

Methods	Design: RCT Country: The Netherlands Accrual dates: 2002 Trial Reg.: NR Funding source: NR
Participants	No. randomised: 48 Inclusion criteria: Localised prostate cancer, informed consent Exclusion criteria: Apparent pre-existing anal irritation, active inflammatory bowel disease, and active bleeding or obstructing haemorrhoids Gender: Male Type of cancer: Prostate Radiotherapy regimen received: 67.5 Gy delivered in 7.5 weeks (4 fractions a week), applying 2.25 Gy daily fractions

	Primary/adjuvant/other: Primary Other treatment received: All participants received 6 months of neoadjuvant hormonal therapy
Interventions	Comparison: ERB vs no ERB Arm 1: Endorectal balloon (ERB) inserted daily before each RT fraction Arm 2: No ERB
Outcomes	GI toxicity: Acute and late (RTOG and Fox Chase Modified Late Effects Tissue Task Force) QoL: NR Other review outcomes: NR Other study outcomes: Urinary toxicity; endoscopic findings Duration of follow-up: Participants were seen weekly during the treatment period and every 3 months afterward. At 3 months, 6 months, 1 year, and 2 years a rectosigmoidoscopy was performed. Acute and late urinary and rectal toxicity items were scored during each visit. Late toxicity was evaluated over the period of the first 30 months after completion of the RT
Notes	Baseline characteristics were not reported Authors concluded that "The ERB significantly reduced the rectal wall volume exposed to doses >40 Gy resulting in reduction of late rectal mucosal changes and reduced late rectal toxicity"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficent detail. "Patients were randomly assigned to receive a treatment with (ERB group, n _ 24) or without ERB (No-ERB group, n _ 24) over a 12-month period during the year 2002"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Insufficient detail to make a judgement but probably unblinded due to the nature of the intervention
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent missing data
Selective reporting (reporting bias)	Low risk	Protocol not seen but expected outcomes were reported

Van Lin 2007 (*Continued*)

Other bias	Unclear risk	Funding and conflicts of interest not declared
Overall judgement	Unclear risk	Due to unclear methodology

Viani 2016

Methods	Design: Open parallel-arm RCT Country: Brazil Trial Reg.: NCT02257827 Accrual dates: November 2009 to January 2013 Funding source: NR
Participants	No. randomised: 215 Inclusion criteria: Men requiring primary treatment of localised prostate cancer Exclusion criteria: Men with metastases, previous prostatectomy, previous RT or chemotherapy or PSA values > 150 ng/ml were excluded Gender: Male Type of cancer: Prostate Other treatment received: Men with intermediate- and high-risk prostate cancer also received androgen blockage with 3.6 mg goserelin acetate for 6 months and 24 months, respectively
Interventions	Comparison: IMRT vs 3DCRT Arm 1: IMRT: 70Gy in 25 fractions (2.8 Gy per day); 5- to 7-field technique Arm 2:3DCRT: 70Gy in 25 fractions (2.8 Gy per day); 6-field technique All participants were simulated in a CT simulator. An enema and 2 glasses of water were recommended before the planning CT. The PTV was created with a 1 cm margin on the CTV except for the rectal wall (0.7 cm) The following dose constraints were used: V50 < 50%; V60 < 35%; V65 < 25%; V70 < 20%; V75 < 15%. All fields were treated daily in a megavoltage linear accelerator (6MV with multileaf collimators)
Outcomes	GI toxicity: acute and late (RTOG) QoL: EORTC QLQPR25 (prostate-specific) Other review outcomes: bowel dose volume Other study outcomes: dosimetric parameters, biochemical control, genitourinary toxicity Duration of follow-up: Median follow-up was 56 months (range 24 - 63). Weekly follow-up during treatment, then "3 to 6 months (evaluation) for the first 5 years". QoL was assessed at 6, 12, 24, and 36 months after treatment
Notes	Group baseline characteristics were similar, including risk group, Gleason score, Initial PSA level, tumour stage, PTV total volume, androgen treatment, and comorbidities (hypertension and diabetes). The median rectal pV54, pV58, and pV62 percentages were 28.2%, 23.4%, and 16.7%, respectively, for 3D-CRT and 21.2.%, 16.3%, and 11.7%, respectively, for IMRT. All differences in RT doses to the OARs between IMRT and 3DCRT favoured IMRT and were statistically significant (P < 0.001). 5-year biochemical control was similar between IMRT and 3DCRT arms (95.4% vs 94.3%)

Viani 2016 (*Continued*)

	Authors emailed for clarification and missing data (18/1/17)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement. "After simulation, patients were sequentially randomized to 1 of the study arms."
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open" RCT
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% missing data
Selective reporting (reporting bias)	Low risk	Expected outcomes reported but protocol not seen
Other bias	Unclear risk	No other sources of potential bias noted. Funding source not declared
Overall judgement	Unclear risk	Mainly as the described trial methodology lacks sufficient detail to make judgements

Vidal-Casariego 2014

Methods	Design: Randomised controlled trial, double-blind Country: Spain Accrual dates: NR Trial Reg.: NCT00828399 Funding source: Financial support: This research has received grants from Fundación de la Sociedad Española de Endocrinología y Nutrición and Consejería de Sanidad (Junta de Castilla y León, SACYL GRS 326/B/08)
Participants	No. randomised: 69 Inclusion criteria: Patients > 18 years for whom RT of the abdominal/pelvic cavity was planned because of a neoplasm in that location, regardless of other cancer treatments (surgery, chemotherapy, brachytherapy), were considered suitable for the trial Exclusion criteria: Life expectancy < 1 year, intestinal failure or short bowel syndrome of any aetiology, relevant intestinal diseases (inflammatory bowel disease, coeliac disease, Whipple disease), moderate or severe chronic kidney disease, or inability to receive oral medication or to understand the provided information

	Gender: 65.2% male Age mean (SD): Intervention 64.9 (9.7), Control: 68.1 (10) Type of cancer: Pelvic or abdominal malignancies (main: urological cancer, gynaecological) Radiotherapy regimen received: NR Primary/adjuvant/other: Primary Other treatment received: Chemotherapy: glutamine arm 44.1% vs placebo 37.1%
Interventions	Comparison: Glutamine vs placebo Arm 1: Glutamine (30 g/day) Investigators recommended the consumption of 3 sachets/day, from 3 days before starting RT and to the completion of it. Each sachet was dissolved in 200 mL of water, and the solution was drunk after a meal Arm 2: Placebo (casein, 30 g/day) Investigators recommended the consumption of 3 sachets/d, from 3 days before starting RT and to the completion of it. Each sachet was dissolved in 200 mL of water, and the solution was drunk after a meal
Outcomes	GI toxicity: Acute RTOG QoL: NR Other review outcomes: NR Other study outcomes: Subjective Global Assessment (SGA), fat and fat-free mass, FFMI, dietary intake, blood tests, tumour markers Duration of follow-up: During RT
Notes	Weight: glutamine arm 74.8 (13.7) vs placebo 68.9 (11.1), P = 0.056

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization, which took place at the time of recruitment, was conducted by the investigator who recruited the patients in a 1:1 ratio to each group by generating a list of random numbers with the software Epidat 3.1"
Allocation concealment (selection bias)	Low risk	Both substances were supplied as a powder for dissolution without flavour, contained in unlabeled sachets of 10 g of product"; "Both glutamine and placebo had similar color, taste, and texture before and after dissolution"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients, the principal investigator, and co-investigators were blinded for treatment assignation and outcomes until the end of the trial, and the blind was broken after the completion of statistical analysis."

Vidal-Casariego 2014 (*Continued*)

Blinding of outcome assessment	Low risk	"Patients, the principal investigator, and co-investigators were blinded for treatment assignation and outcomes until the end of the trial, and the blind was broken after the completion of statistical analysis."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"An intention-to-treat analysis was performed"; "During follow-up, 1 patient in the former group dropped out the trial due to complications from an underlying disease."
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None noted
Overall judgement	Low risk	Low risk overall

Wedlake 2012

Methods	Design: 3-arm, nonblinded, multicentre randomised controlled trial Country: England Accrual dates: January 2006 to July 2009 Trial Reg.: NR Funding source: SHS International (Liverpool, UK) provided the Liquigen supplements and an unrestricted educational grant to cover partial funding of the present study. We acknowledge NHS funding to the NIHR Biomedical Research Centre
Participants	No. randomised: 117 Inclusion criteria: Patients with a histologically-proven gynaecological, urological or lower gastrointestinal malignancy due to receive radical (long course) EBRT were eligible Exclusion criteria: NR Gender: 67.5% male Age: Intervention 1: 65 (mean) 10.6 SD, Intervention 2: 64 (mean) 11.4 SD, Control: 65 (mean) 11.3 SD Type of cancer: 48% urological; 32% gastrointestinal; 20% gynaecological Radiotherapy regimen received: 54 Gy to 64 Gy in standard fractionation Primary/adjuvant/other: Primary Other treatment received: 50% of participants received concomitant chemotherapy
Interventions	Comparison: Low or modified fat diet vs control Arm 1: Group 1 (low fat) was prescribed a low-fat diet with LCT dietary fats calculated to comprise 20% of total energy intake, with the aim being to reduce the volume of potentially pro-inflammatory fat substrates and minimise the stimulation of bile and pancreatic secretions Arm 2: Group 2 (modified fat) was prescribed a diet with fats calculated to comprise 40% of total energy intake. However, 50% was to be derived from LCT dietary fats and 50% as the MCT-based fat emulsion 'Liquigen' (SHS Interna- tional, Liverpool, UK)

	providing 1883 kJ (450 kcal) per 100 mL Arm 3: Group 3 (normal fat), the control arm was prescribed a normal fat diet with LCT dietary fats calculated to comprise 40% of total energy
Outcomes	GI toxicity: Acute RTOG/EORTC QoL: IBDQ Other review outcomes: NR Other study outcomes: Change in weight (baseline to 4 weeks) Duration of follow-up: During and up to 1 year post-RT
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The independent Institute of Cancer Research, Randomisation Office, randomised patients using permuted block
Allocation concealment (selection bias)	Low risk	The independent Institute of Cancer Research, Randomisation Office, randomised patients using permuted block
Blinding of participants and personnel (performance bias) All outcomes	High risk	Allocation group unblinded to participants and investigators
Blinding of outcome assessment	High risk	Allocation group unblinded to analysts
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	For acute data, low risk of bias with only 9% (10/117) of participants with non-evaluable data. For 6- - 12-month data, high risk of bias with 35% attrition (75/117 only with evaluable data) at 1 year
Selective reporting (reporting bias)	Low risk	All outcomes stated and reported
Other bias	High risk	Low risk in baseline factors (e.g. pelvic site, receipt of chemotherapy, age) which were balanced between groups. But high risk in low fat + Liquigen group: only 42% achieved 100% compliance with Liquigen prescription
Overall judgement	High risk	In the normal-fat group (LCTs comprising 40% of total energy) only 24% of men and 30% of women achieved the presecribed LCT-based fat intake

Wedlake 2017

Methods	Design: Multicentre randomised controlled trial Country: England UK Accrual dates: December 2009 to December 2013 Trial Reg.: NCT01170299 Funding source: The Royal Marsden Cancer Charity, National Institute for Health Research (NIHR) to the Royal Marsden / Institute of Cancer Research (ICR), Biomedical Research Centre (BRC)
Participants	No. randomised: 166 Inclusion criteria: Patients receiving radical (≥ 45 Gy) RT for histologically-proven lower gastrointestinal (anal, colon, rectal) or gynaecological malignancies, with or without concommitant chemotherapy and able to tolerate 100% oral diet Patients undergo RT once daily comprising approximately 25 (or more) fractions in total, delivered for 5 - 7 weeks in the absence of unacceptable toxicity Exclusion criteria: Established wheat intolerance, coeliac disease, a gastrointestinal stent or stoma, or enrolled in other trials with conflicting end points Gender: 42% male Age median (range): Intervention 1: 62 (26 - 91), Intervention 2: 64 (28 - 87), Control: 63 (35 - 88) Type of cancer: Gastrointestinal or gynaecological malignancies Radiotherapy regimen received: Median RT dose: 50.4 Gy Primary/adjuvant/other: Primary Other treatment received: 72% concomitant chemotherapy
Interventions	Comparison: High fibre vs low fibre vs habitual fibre diet Arm A: High-fibre diet (target > 18 g/day non-starch polysaccharide) to be implemented from the first to the last day of RT treatment Arm B: Low-fibre diet (< 10 g/day non-starch polysaccharide) to be implemented from the first to the last day of RT treatment Arm C: Habitual fibre diet (control) continued throughout RT treatment (no intervention)
Outcomes	GI toxicity: Royal Marsden Stool Questionnaire recording daily stool frequency, stool form (using Bristol Stool Chart), number of loose stool days and number of medication days. Mean stool frequency and consistency by group. Toxicity evaluation including change in IBDQ-B score between baseline (i.e. Day 1 of radiotherapy treatment) and the nadir score during treatment; incidence of toxicity (using Bristol Stool Chart); QoL: IBDQ Other review outcomes: NR Other study outcomes: NR Duration of follow-up: Costs for symptom management
Notes	Change in faecal Short Chain Fatty Acids (SCFA) between start and end of RT measured in a subgroup of participants to evaluate possible association with fibre intake Participants were stratified according to disease (gynaecological vs gastrointestinal) and concomitant therapy (received vs not received)
Risk of bias	

Wedlake 2017 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomised by the independent Institute of Cancer Research (ICR) using the minimisation method, stratified for chemotherapy and pelvic site
Allocation concealment (selection bias)	Low risk	Allocation by telephone to named investigator
Blinding of participants and personnel (performance bias) All outcomes	High risk	Intervention unblinded to participants and investigators
Blinding of outcome assessment	High risk	Intervention unblinded to outcome assessors and analysts
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% participants not available for analysis at end of RT, 21% not available at 1 year
Selective reporting (reporting bias)	Low risk	All outcomes reported aside from cost analysis, which was not reported due to poor participant recall and which would not have biased the primary/secondary end points
Other bias	Low risk	Study groups maintained compliance with fibre targets and thus the planned differential in intake. Time spent with dietitian was balanced across all groups to minimise placebo effect
Overall judgement	Low risk	Based on above

Yu 2015

Methods	Design: Open parallel-arm RCT Country: China Trial Reg.: NR Accrual dates: September 2006 to September 2009 Funding source: Huai'an Science and Technology Bureau (no. HAS201030)
Participants	No. randomised: 72 Inclusion criteria: Women with squamous cell cervical cancer; 18 to 70 years old; stage IIA to IIIB; requiring primary treatment; normal haematological and liver function tests; no history of chemoradiotherapy; signed informed consent Exclusion criteria: NR Gender: Female

Yu 2015 (*Continued*)

	Type of cancer: Cervix Other treatment received: All participants received concurrent chemotherapy of nedaplatin 30 mg/m^2 weekly for 6 cycles with an afterload of RT of 6 Gy in 6 fractions each time. If needed granulocyte colony stimulating factor was used for symptomatic treatment
Interventions	Comparison: IMRT vs 3DCRT Arm 1: IMRT: 45 Gy in 22 fractions to the primary lesions, 50 Gy in 22 fractions to the pelvic wall lymphatic drainage area. The dose gradient PTV was ≤ 10%; rectum V40 < 40%; small bowel V40 < 30% Arm 2: 3DCRT: 45 Gy in 22 fractions to pelvis with subsequent supplement of 6.0 Gy in 3 fractions to the centre "while sheltering the pelvic wall" "During therapy, patients were supine with hands clasped and elbows and legs naturally closed." All participants underwent CT simulation. The bladder was emptied 90 minutes before the scan and then filled with meglutamine diatrizoate injection. The scan was started after an injection of iohexol. PTV was created with a 1 cm margin on the CTV
Outcomes	GI toxicity: Acute and late (CTCAE v 3) QoL: NR Other review outcomes: NR Other study outcomes: OS and DFS Duration of follow-up: 3-monthly in year 1, 6-monthly in year 2, thereafter once a year
Notes	Baseline characteristics, including age, histological type of cancer (mainly squamous), performance status and FIGO staging were similar between IMRT and 3DCRT arms. OS and DFS outcomes were also similar

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomly divided into two groups by the envelope method"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open" RCT
Blinding of outcome assessment	Unclear risk	Breaking the randomisation code and outcome assessor blinding is not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement. Withdrawals and attrition not described
Selective reporting (reporting bias)	Unclear risk	Late toxicity and median follow-up was not reported

Yu 2015 (*Continued*)

Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Mainly as the described trial methodology lacks sufficient detail to make judgements and some expected outcomes have not yet been reported

Zachariah 2010

Methods	Design: Randomised, double-blinded, placebo-controlled trial Country: USA Accrual dates: December 2003 to February 2006 Trial Reg.: NR Funding source: The trial and the publication of the results are supported in part by grants RTOG U10 CA21661, CCOP U10 CA37422, and Stat U10 CA32115 to the Radiation Therapy Oncology Group (RTOG) from the National Cancer Institute and Novartis
Participants	No. randomised: 233 Inclusion criteria: Patients receiving concurrent chemotherapy and pelvic radiation therapy for rectal or anal cancer Exclusion criteria: Patients with prior pelvic irradiation, hyperfractionated RT, split-course RT, intensity-modulated RT, and/or planned brachytherapy before completion of EBRT, known allergy/hypersensitivity to octreotide acetate or other related drugs/compounds, previously received octreotide acetate for cancer therapy-related diarrhoea; a history of chronic or acute regional enteritis, malabsorption syndrome(s), or other history of inflammatory bowel disease; uncontrolled diabetes and cholecystitis or gallstones (unless cholecystectomy was performed); colostomy or abdominoperineal resection or other surgery leaving the patient without a functioning rectum; incontinence of stool or uncontrolled diarrhoea (> grade 2 CTCAE v3.0) at baseline; pregnant or lactating women; a history of hepatic disease; HIV-positive Gender: 63% male Age median (range): Intervention: 61 (27 - 83), Control: 61 (37 - 85) Type of cancer: Rectal and anal cancers - mostly rectal cancer (80%) Radiotherapy regimen received: 45 Gy standard fractionation Primary/adjuvant/other: Primary Other treatment received: The chemotherapy regimen was by institutional choice
Interventions	Comparison: Long-acting octreotide acetate (LAO) vs placebo Arm 1: 2 30 mg intramuscular injections of LAO; Participants who demonstrated tolerance received the first dose of study drug between 4 and 7 days before the start of radiation, because a latent period before the drug was expected to be fully effective. The second dose of study drug was given on day 22 (± 3 days) of radiation Arm 2: Placebo
Outcomes	GI toxicity: Late 4-item Diarrhea Assessment Scale (DAS) QoL: 24-item health-related Quality of Life-Radiation Therapy Instrument (QOL-RTI) Other review outcomes: NR

	Other study outcomes: 14-item Expanded Prostate Cancer Index Bowel (EPIC-Bowel), the7-item Functional Alterations due to Changes in Elimination Bowel (FACE-Bowel) Duration of follow-up: 15 months	
Notes	None	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed using the Zelen (33) treatment allocation scheme to balance patient factors and institution."
Allocation concealment (selection bias)	Low risk	"Randomization was performed using the Zelen (33) treatment allocation scheme to balance patient factors and institution."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement
Overall judgement	Unclear risk	Insufficient detail to make a judgement

ABBREVIATIONS:
5-FU = 5-fluorouracil
ALT = alanine transaminase
AST = aspartate transaminase
ASA = aminosalicylic acid
BDP = beclomethasone dipropionate
BMI = body mass index
BT = brachytherapy
CFU = colony-forming unit
CTCAE = Common Terminology Criteria for Adverse Events
DFS = disease-free survival
EBRT = electron beam radiotherapy
ECOG = Easter Cooperative Oncoly Group
FFMI = fat-free mass index
FFQ = food frequency questionnaire

HBOT = hyperbaric oxygen therapy
IBD = irritable bowel disease
IBS = irritable bowel syndrome
IGRT = image guided RT
i.m. = intramuscular
i.v. = intravenous
LHRH = luteinising hormone-releasing hormone
MRI = magnetic resonance imaging
NR = not reported
OAR = organs at risk
OS = overall survival
POMS - profile of moods state
PRS = progression-free survival
PSA = prostate-specific antigen
PTV = planning target volume
QoL = quality of life
RBE = relative biological effectiveness
RCT = randomised controlled trial
RT = radiotherapy
RTOG = Radiation Therap Oncology Group
SOD = superoxide dismutase
sRT = standard radiotherapy
TAH = total abdominal hysterectomy
TURB = transurethral resection of bladder
VBT = vascular brachytherapy

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akhtar 2010	Ineligible study design
Al-Mamgani 2008	Ineligible intervention (dose escalation study)
Al-Mamgani 2009	Ineligible study design
Barnett 2011	Ineligible study design
Barraclough 2012	Ineligible study design
Basu 2016	Ineligible comparator (chemotherapy)
Becker-Schiebe 2016	Ineligible study design
Belcaro 2008	Ineligible study design
Birgisson 2006	Ineligible intervention

(*Continued*)

Bittner 2008	Ineligible study design
Boronow 1977	Ineligible intervention (out of date)
Bossi 2016	Ineligible study design
Bounous 1975	Ineligible study design
Brabbins 2005	Ineligible intervention (dose escalation study)
Brennan 2015	Ineligible study design
Bruner 2015	Ineligible study design
Capirci 2001	Ineligible study design
Chen 2012	Ineligible study design
Dische 1999	Ineligible intervention (hyperbaric oxygen in addition to RT was intended to improve survival not reduce toxicity)
Dunst 2000	Ineligible study design
Frøseth 2015	Ineligible outcomes
Fuccio 2013	Editorial
Ghaly 2003	Ineligible intervention
Guix 2010	Ineligible intervention (dose escalation study)
Hamilton-Reeves 2013	Ineligible participant population
Ishii 2016	Ineligible study design
Kavikondala 2016	Ineligible intervention
Khan 2000	Fewer than 20 participants
Kilic 2012	Ineligible study design
Kim 2016	Ineligible study design
Koizumi 2005	Ineligible study design
Kucuktulu 2013	Ineligible study design

(*Continued*)

Morton 2016	Ineligible intervention (altered fractionation schedules)
Nguyen 1998	Ineligible comparator (70 Gy versus 78 Gy compared)
Nout 2011	Ineligible comparator (RT vs no RT)
Olofsen-Van 2001	Ineligible study design
Pollack 1996	Ineligible comparator (same as Nguyen 1998)
Reinshagen 2012	Fewer than 20 participants
Restivo 2015	Ineligible outcomes
Roscoe 2009	Ineligible outcomes
Sheng 2013	Ineligible participant population
Sirak 2014	Ineligible study design
Sorbe 2012a	Ineligible intervention (dose escalation study)
Sorbe 2012b	Ineligible intervention (dose escalation study)
Stojcev 2013	Ineligible study design
Sun 2014	A review
Tacev 2005	Ineligible intervention - dose-escalation study
Teshima 1990	Ineligible participant population
Timko 2013	Ineligible study design
Uhl 2013	Ineligible study design
Ungerleider 1984	Ineligible study design
Urbancsek 2001	Ineligible participant population
Vuong 2014	Ineligible study design
Widmark 1997	Ineligible study design
Wortel 2015	Ineligible study design

(*Continued*)

Wortel 2016	Ineligible study design
Yoshioka 2014	Ineligible study design
Zapatero 2010	Fewer than 20 participants
Zilli 2015	Ineligible intervention (altered fractionation schedules)

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ni 2017

Methods	Title states 'a randomised study'; abstract text states 'A prospective investigation study was conducted"
Participants	183 women receiving adjuvant RT for cervical or endometrial cancers
Interventions	IMRT vs 3DCRT
Outcomes	Dosimetric parameters; acute radiation injury to bowel, bladder and bone marrow; and QOL
Notes	Authors concluded in the abstract that "IMRT has shown that there are significant benefit(s) for the post-operative patients with cervical cancer and endometrial cancer compared to 3D-CRT"

Characteristics of ongoing studies *[ordered by study ID]*

Asadpour 2017

Trial name or title	Randomised study exploring the combination of radiotherapy with two types of acupuncture treatment (ROSETTA): study protocol for a randomised controlled trial
Methods	Phase II RCT Trial name: ROSETTA Reg ID: NCT02674646
Participants	74 patients 18 or over receiving radiotherapy. Need to be able to understand the clinical trial and give written informed consent. Excluded if acupuncture contraindicated, known coagulopathy or anticoagulation treatment, missing compliance, skin disease in region of acupuncture treatment, participation in another clinical trial
Interventions	Verum (traditional) acupuncture vs false (sham) acupuncture
Outcomes	Fatigue, QOL, headache, nausea, skin erythema
Starting date	2016

Asadpour 2017 (*Continued*)

Contact information	stephanie.combs@tum.de
Notes	This trial will include "patients with tumours treated by RT in various anatomical regions", therefore, it is unclear how many of these will be primary pelvic cancers

NCT00326638

Trial name or title	Randomised phase III trial of 3D conformal radiotherapy versus helical tomotherapy IMRT in high-risk prostate cancer
Methods	Open-label, parallel-arm RCT Country: Canada
Participants	72 men with high-risk prostate cancer
Interventions	Arm A: 3DCRT 7800 cGy/39 fractions once daily Monday to Friday for 8 weeks Arm B: IMRT 7800 cGY/39 fractions once daily Monday to Friday for 8 weeks
Outcomes	Primary: Late rectal toxicity Secondary: Acute rectal toxicity, acute and late bladder toxicity, disease-specific survival at 5 years, biochemical relapse free survival at 5 years, local control rates at 5 years, QoL Time points for follow-up: Month 1, 4, 8, every 4 months during years 1 - 2, then every 6 months during years 2 - 5, then every 12 months until disease progression
Starting date	March 2005
Contact information	Ottawa Hospital Research Institute: Shawn Malone
Notes	Estimated study completion date: March 2018

NCT00807768

Trial name or title	A phase III trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy in patients with high risk, early stage endometrial carcinoma
Methods	Open-label, parallel-arm RCT Country: USA
Participants	555 women with high-risk, early-stage endometrial cancer
Interventions	Arm A: Pelvic RT (either 3DCRT or IMRT) 5 days a week, for 5 - 6 weeks (total of 25 - 28 fractions) Arm B: Vaginal cuff BT comprising 3 - 5 high-dose rate treatments over approximately 2 weeks or 1 or 2 low-dose rate brachytherapy treatments over 1 - 2 days. Beginning within 3 weeks after initiating brachytherapy, participants receive paclitaxel IV over 3 hours and carboplatin IV over 30 - 60 minutes on day 1. Chemotherapy repeats every 21 days for up to 3 courses

NCT00807768 (*Continued*)

Outcomes	Primary: rRcurrence-free survival Secondary: Contributing cause of death, extra-pelvic recurrence, pelvic/vaginal recurrence, overall survival Other outcomes: Frequency and severity of late adverse effects assessed by the CTCAE v.3.0 Timeframe for follow-up: every 3 months for 2 years, every 6 months for 3 years, and then annually for up to 5 years
Starting date	March 2009
Contact information	Gynecologic Oncology Group: Marcus Randall
Notes	Estimated study completion date: December 2014

NCT01164150

Trial name or title	Prospective randomised phase II trial evaluating adjuvant pelvic radiotherapy using either IMRT or 3-dimensional Planning for endometrial cancer. ICORG 09-06
Methods	Open-label, parallel-arm RCT Country: Ireland
Participants	154 women with endometrial cancer post-surgery requiring adjuvant RT
Interventions	Arm A: 3DCRT (45 Gy/25 fractions) + (11 Gy/2 fractions) brachytherapy Arm B: IMRT (45 Gy/25 fractions) + (11 Gy/2 fractions) brachytherapy
Outcomes	Primary: Incidence of ≥ grade 2 acute genitourinary (GU) and gastrointestinal (GI) toxicity according to NCI CTCAE v.3.0 Secondary: Incidence of late GI and GU toxicity according to NCI CTCAE v.3.0 Feasibility of implementing pelvic nodal irradiation using intensity-modulated radiotherapy in gynaecological cancer Establishment of an image-guided pathway for gynaecological cancer radiotherapy Rate of locoregional control as assessed by CT scan, MRI, and biopsy QoL as assessed using EORTC QLQ-C30 and EORTC QLQ Cervical Cancer Specific Module CX 24 questionnaires Overall survival rate
Starting date	March 2010
Contact information	Charles.Gillham@slh.ie
Notes	Estimated study completion date: December 2023

NCT01641497

Trial name or title	Phase III study comparing 3D conformal radiotherapy and conformal radiotherapy IMRT to treat endometrial cancer of 70 Years old women : contribution of oncogeriatric evaluation to the study of acute toxicity
Methods	Open-label, parallel-arm RCT Country: France
Participants	60 women 70 years and older with endometrial cancer
Interventions	Arm A: 3DCRT 25 fractions of 1.8 Gy in 5 weeks (45 Gy total) Arm B: IMRT 25 fractions of 1.8 Gy in 5 weeks (45 Gy total)
Outcomes	Primary: Change from baseline in acute toxicity all along the radiation; CTCAE v 4.0 > grade 2 (baseline, Day 5, Day 10, Day 15, Day 20, Day 25, 1 week and 8 weeks after end of treatment) Secondary: Geriatric intervention; geriatric repercussion (activities in daily living, mini-nutritional assessment, geriatric depression scale and other); duration of radiation; QoL; late major toxicity progression-free survival
Starting date	May 2012
Contact information	Centre Oscar Lambret: Florence Le Tinier
Notes	Estimated study completion date: March 2017

NCT01672892

Trial name or title	A randomised phase III study of standard vs. IMRT pelvic radiation for post-operative treatment of endometrial and cervical cancer (TIME-C)
Methods	Open-label, parallel-arm RCT Country: USA
Participants	289 women requiring postoperative RT for endometrial or cervical cancer
Interventions	Arm A: 3DCRT 5 days a week for up to 5.5 weeks Arm B: IMRT 5 days a week for up to 5.5 weeks
Outcomes	Primary: Acute GI toxicity, as measured by bowel domain of EPIC (Time frame: week 5 of RT) Secondary: Validation of EPIC bowel domains, toxicity as measured by CTCAE v.4.0; urinary toxicity; QoL, health utilities; locoregional control (Time frame: before study start, week 3 of RT, week 5 of RT, 4 - 6 weeks after RT, 1 year from start of RT and 3 years from start of RT)
Starting date	November 2012
Contact information	Radiation Therapy Oncology Group: Ann Klopp
Notes	Estimated study completion date: December 2015

NCT01706393

Trial name or title	Double blind placebo controlled randomised trial on effects of probiotics supplementation on intestinal microbiome in malignancy patients who get pelvic/abdominal radiotherapy
Methods	Double-blind, parallel-arm RCT Country: South Korea
Participants	26 patients receiving pelvic/abdominal RT
Interventions	Arm A: Probiotics - 1 tablet twice a day for 6 weeks (including during 5 weeks of RT) Arm 2: Identical placebo
Outcomes	Primary: Change in intestinal microbiome Secondary: Diarrhoea (according to CTCAE) and GI symptoms (GSRS)
Starting date	October 2012
Contact information	Seoul National University Hospital: Hak Jae Kim (khjae@snu.ac.kr) Seung Wan Kang (drdemian@snu.ac.kr)
Notes	Estimated study completion date: July 2013 (Emailed 4th October 2016 for more info)

NCT01790035

Trial name or title	A phase I and randomised controlled phase II trial of the probiotic LGG for prevention of side effects in patients undergoing chemoradiation for gastrointestinal cancer
Methods	Double-blind, parallel-arm RCT Country: USA
Participants	120 patients with GI cancer
Interventions	Arm A: Probiotic LGG 1 tablet twice a day Arm B: Placebo
Outcomes	Primary: Grade 2 or more diarrhoea (CTCAE) (time frame: up to 6 months) Secondary: Diarrhoea score (FACIT-D), need for anti-diarrhoeal medication, grade 3 or more diarrhoea, faecal calprotectin, serum citrulline
Starting date	August 2014
Contact information	Washington University School of Medicine: Matthew Ciorba (mciorba@wustl.edu)
Notes	Estimated study completion date: October 2021

NCT01839994

Trial name or title	Phase III clinical trial on conventionally fractionated conformal radiotherapy (CF-CRT) versus CF-CRT combined With High-dose-rate brachytherapy or stereotactic body radiotherapy for intermediate and high-risk prostate cancer
Methods	Open-label, parallel-arm RCT Country: Poland
Participants	350 patients with intermediate and high-risk prostate cancer
Interventions	Arm A: Conventionally-fractionated CRT (IMRT or Rapid Arc) to the TD of 50 Gy, 5 days a week over the period of 5 weeks, AND 2 10 Gy fractions of real- time HDR brachytherapy OR 2 SBRT boosts of 10 Gy per fraction Arm B: Conventionally-fractionated CRT (IMRT or Rapid Arc) to the TD of 50 Gy, 5 days a week over the period of 5 weeks, followed by a boost to the prostate (26 or 28 Gy in 2.0 Gy per fraction 5 days a week over the period of 2.5 weeks) to the total dose of 76 or 78 Gy
Outcomes	Primary: Biochemical failure Secondary: Local relapse, locoregional relapse, incidence and severity of acute and late toxicity (CTCAE and RTOG/EORTC scoring system), overall survival, progression-free survival Time frame: 3 - 5 years
Starting date	June 2013
Contact information	Maria Sklodowska-Curie Memorial Cancer Center, Institute of Oncology: Katarzyna Behrendt (kbehrendt@io.gliwice.pl); Rafa Suwi ski (rafals@io.gliwice.pl)
Notes	Estimated study completion date: December 2018 (primary outcome December 2016)

NCT02151019

Trial name or title	Randomised phase II study of preoperative 3-D conformal radiotherapy (3-DCRT) versus Intensity Modulated Radiotherapy (IMRT) for locally advanced rectal cancer
Methods	Open-label, parallel-arm RCT Country: Ireland
Participants	268 patients with locally advanced rectal cancer
Interventions	Arm A: IMRT with 50.4 Gy / 28 fraction Arm B: 3DCRT with 50.4 Gy / 28 fraction
Outcomes	Primary: Acute grade 2 or more GI toxicity (CTCAE v.4) Secondary: Acute GU toxicity, late GI and GU toxicity, locoregional control, QoL (EORTC QLQ-C30 and QLQ-CR29), disease-free survival, overall survival Acute toxicities will be assessed weekly during radiotherapy, and at 2 and 4 weeks post-treatment Late toxicities will be assessed at 3, 6, 9, 12, 18, 24 months post-treatment, and annually to 10 years
Starting date	August 2014

NCT02151019 (*Continued*)

Contact information	Cancer Trials Ireland: Brian O'Neill
Notes	Estimated study completion date: July 2030 (primary outcome August 2020)

NCT02351089

Trial name or title	Probiotics in radiation-treated gynaecologic cancer
Methods	Double-blind, parallel-arm RCT Country: Sweden
Participants	200 women with gynaecological cancer undergoing primary or postoperative RT
Interventions	Arm A: Probiotic capsule Arm B: Placebo
Outcomes	Primary: Change in incidence of loose/watery stools (baseline to 10 weeks) Secondary: Not stated
Starting date	February 2015
Contact information	Department of Oncology, Lund, Sweden: Maria Bjurberg (maria.bjurberg@skane.se)
Notes	Estimated study completion date: December 2016

NCT02516501

Trial name or title	Investigating the impact of a ketogenic diet intervention during radiotherapy on body composition: a pilot trial
Methods	Open-label, phase I, parallel-arm RCT Country: Germany
Participants	85 patients with either colorectal, breast, or head and neck tumours
Interventions	Arm A: Before RT, after overnight fast, a ketogenic breakfast consisting of (i) up to 250 ml of a medium chain triglyceride drink (betaquick, vitaflo) plus (ii) 5 g, 10 g or 15 g amino acids (MAP, dr. reinwald gmbh+co kg) Arm B: Control group that will not receive advice to follow a ketogenic diet or reduce carbohydrates
Outcomes	Primary: Feasibility of ketogenic diet (measured by dropout rates), change in body weight, body composition, BIA phase angle Secondary:QoL (EORTC QLQ-C30), toxicities, blood parameters, regression at time of surgery in case of rectum carcinomas Time frame: up to 12 weeks after RT
Starting date	June 2015

NCT02516501 (*Continued*)

Contact information	Department of Radiotherapy and Radiation Oncology, Scheinfurt, Bavaria, Germany. Reinhart Sweeney (rsweeney@leopoldina.de)
Notes	Estimated study completion date: June 2018

3DCRT: three-dimensional conformal radiotherapy
CT: computed tomography
GI: gastrointestinal
GU: genito-urinary
IMRT: intensity modulated radiotherapy
QoL: quality of life
RT: radiotherapy

DATA AND ANALYSES

Comparison 1. Conformal RT vs conventional RT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+	2	307	Risk Ratio (IV, Random, 95% CI)	0.57 [0.40, 0.82]
1.1 3DCRT vs conRT	1	263	Risk Ratio (IV, Random, 95% CI)	0.60 [0.39, 0.93]
1.2 IMRT vs conRT	1	44	Risk Ratio (IV, Random, 95% CI)	0.5 [0.25, 1.00]
2 Late GI toxicity: grade 2+	3	517	Risk Ratio (IV, Random, 95% CI)	0.49 [0.22, 1.09]
2.1 3DCRT vs conRT	2	473	Risk Ratio (IV, Random, 95% CI)	0.56 [0.23, 1.35]
2.2 IMRT vs conRT	1	44	Risk Ratio (IV, Random, 95% CI)	0.2 [0.03, 1.58]
3 Acute GI toxicity: grade 1+	2	307	Risk Ratio (IV, Random, 95% CI)	0.75 [0.42, 1.36]
3.1 3DCRT vs conRT	1	263	Risk Ratio (IV, Random, 95% CI)	0.94 [0.85, 1.04]
3.2 IMRT vs conRT	1	44	Risk Ratio (IV, Random, 95% CI)	0.5 [0.25, 1.00]
4 Late GI toxicity: grade 1+	2	292	Risk Ratio (IV, Random, 95% CI)	0.55 [0.19, 1.59]
4.1 3DCRT vs conRT	1	248	Risk Ratio (IV, Random, 95% CI)	0.84 [0.68, 1.04]
4.2 IMRT vs conRT	1	44	Risk Ratio (IV, Random, 95% CI)	0.27 [0.09, 0.85]
5 Vomiting: grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5.1 IMRT vs conRT	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Medication for GI symptom control	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6.1 3DCRT vs conRT	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. IMRT vs 3DCRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 GI symptom score (6 months)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Urological cancer	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 GI symptom score (2 years)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Urological cancer	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Acute GI toxicity: grade 2+	4	444	Risk Ratio (IV, Random, 95% CI)	0.48 [0.26, 0.88]
3.1 Gynaecological cancer	3	229	Risk Ratio (IV, Random, 95% CI)	0.54 [0.28, 1.07]
3.2 Urological cancer	1	215	Risk Ratio (IV, Random, 95% CI)	0.31 [0.15, 0.66]
4 Late GI toxicity: grade 2+	2	332	Risk Ratio (IV, Random, 95% CI)	0.37 [0.21, 0.65]
4.1 Gynaecological cancer	1	117	Risk Ratio (IV, Random, 95% CI)	0.46 [0.20, 1.05]
4.2 Urological cancer	1	215	Risk Ratio (IV, Random, 95% CI)	0.30 [0.13, 0.66]
5 Acute GI toxicity: grade 1+	4	444	Risk Ratio (IV, Random, 95% CI)	0.59 [0.41, 0.86]
5.1 Gynaecological cancer	3	229	Risk Ratio (IV, Random, 95% CI)	0.67 [0.48, 0.95]
5.2 Urological cancer	1	215	Risk Ratio (IV, Random, 95% CI)	0.31 [0.15, 0.66]
6 Late GI toxicity: grade 1+	2	332	Risk Ratio (IV, Random, 95% CI)	0.65 [0.46, 0.93]
6.1 Urological cancer	1	215	Risk Ratio (IV, Random, 95% CI)	0.71 [0.47, 1.05]
6.2 Gynaecological cancer	1	117	Risk Ratio (IV, Random, 95% CI)	0.46 [0.20, 1.05]
7 Diarrhoea: grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7.1 Gynaecological cancer	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

8 Vomiting: grade 2+	2	112	Risk Ratio (IV, Random, 95% CI)	0.60 [0.29, 1.24]
8.1 Gynaecological cancer	2	112	Risk Ratio (IV, Random, 95% CI)	0.60 [0.29, 1.24]

Comparison 3. Brachytherapy vs EBRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Gynaecological cancer	1	423	Risk Ratio (IV, Random, 95% CI)	0.02 [0.00, 0.18]
1.2 Urological cancer	1	20	Risk Ratio (IV, Random, 95% CI)	0.33 [0.04, 2.69]
2 Late GI toxicity: grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.1 Gynaecological cancer	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Acute GI toxicity: grade 1	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1 Gynaecological cancer	1	423	Risk Ratio (IV, Random, 95% CI)	0.33 [0.22, 0.50]
3.2 Urological cancer	1	20	Risk Ratio (IV, Random, 95% CI)	0.75 [0.22, 2.52]
4 Late GI toxicity: grade 1	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4.1 Gynaecological cancer	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Treatment discontinuation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5.1 Gynaecological cancer	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Reduced dose volume vs standard dose volume

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Acute GI toxicity: grade 1+	3	354	Risk Ratio (IV, Random, 95% CI)	0.61 [0.34, 1.10]
3 Late GI toxicity: grade 2+ (1 year post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Late GI toxicity: grade 2+ (2 years post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Late GI toxicity: grade 1+	2	154	Risk Ratio (IV, Random, 95% CI)	1.15 [0.49, 2.68]

Comparison 5. Higher BV prep vs lower BV prep

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Acute GI toxicity: grade 1+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Late GI toxicity: grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Late GI toxicity: grade 1+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 6. Evening RT vs morning RT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity (diarrhoea): grade 2+ (during RT)	2	294	Risk Ratio (IV, Random, 95% CI)	0.51 [0.34, 0.76]
2 Acute GI toxicity (diarrhoea): grade 1+ (during RT)	2	294	Risk Ratio (IV, Random, 95% CI)	0.78 [0.68, 0.89]
3 Vomiting grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 7. Perineal hydrogel spacer vs no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+	2	289	Risk Ratio (IV, Random, 95% CI)	0.51 [0.08, 3.38]
2 Acute GI toxicity: grade 1+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Late GI toxicity: grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3.1 15 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 3 years	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Late GI toxicity: grade 1+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4.1 15 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 3 years	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Rectal bleeding (late)	2	289	Risk Ratio (IV, Random, 95% CI)	0.25 [0.03, 1.84]
6 Rectal pain (acute)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 8. Endorectal balloon vs no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Acute GI toxicity: grade 1+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Late GI toxicity: grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Late GI toxicity: grade 1+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Diarrhoea (late)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Rectal bleeding (acute)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Rectal bleeding (late)	2	91	Risk Ratio (IV, Random, 95% CI)	0.53 [0.25, 1.09]

Comparison 9. Aminosalicylates vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+ (during RT)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Mesalazine	2	143	Risk Ratio (IV, Random, 95% CI)	1.22 [1.02, 1.45]
1.2 Sulfasalazine	2	182	Risk Ratio (IV, Random, 95% CI)	0.29 [0.11, 0.75]
2 Acute GI toxicity: grade 1+ (during RT)	2	182	Risk Ratio (IV, Random, 95% CI)	0.74 [0.52, 1.05]
2.1 Sulfasalazine	2	182	Risk Ratio (IV, Random, 95% CI)	0.74 [0.52, 1.05]
3 Diarrhoea grade 2+(during RT)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1 Mesalazine	2	191	Risk Ratio (IV, Random, 95% CI)	1.55 [1.14, 2.10]
3.2 Sulfasalazine	2	171	Risk Ratio (IV, Random, 95% CI)	0.80 [0.41, 1.58]
3.3 Olsalazine	1	58	Risk Ratio (IV, Random, 95% CI)	1.70 [1.00, 2.87]
4 Diarrhoea grade 2+(up to 3 months)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4.1 Sulfasalazine	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Rectal bleeding grade 2+ (during RT)	2	142	Risk Ratio (IV, Random, 95% CI)	0.76 [0.47, 1.24]
5.1 Sulfasalazine	1	84	Risk Ratio (IV, Random, 95% CI)	0.8 [0.49, 1.32]
5.2 Olsalazine	1	58	Risk Ratio (IV, Random, 95% CI)	0.31 [0.03, 2.82]
6 Rectal bleeding grade 2+ (up to 3 months)	1	84	Risk Ratio (IV, Random, 95% CI)	0.8 [0.49, 1.32]
6.1 Sulfasalazine	1	84	Risk Ratio (IV, Random, 95% CI)	0.8 [0.49, 1.32]
7 Pain/cramps grade 2+(during RT)	3	261	Risk Ratio (IV, Random, 95% CI)	1.08 [0.50, 2.33]
7.1 Mesalazine	1	119	Risk Ratio (IV, Random, 95% CI)	0.67 [0.43, 1.04]
7.2 Sulfasalazine	1	84	Risk Ratio (IV, Random, 95% CI)	1.5 [0.46, 4.93]
7.3 Olsalazine	1	58	Risk Ratio (IV, Random, 95% CI)	2.18 [0.62, 7.61]
8 Pain/cramps grade 2+(up to 3 months)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8.1 Sulfasalazine	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9 Tenesmus grade 2+(during RT)	2	142	Risk Ratio (IV, Random, 95% CI)	2.10 [0.73, 6.03]
9.1 Sulfasalazine	1	84	Risk Ratio (IV, Random, 95% CI)	3.0 [0.87, 10.31]
9.2 Olsalazine	1	58	Risk Ratio (IV, Random, 95% CI)	0.93 [0.14, 6.18]
10 Tenesmus grade 2+(up to 3 months)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
10.1 Sulfasalazine	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 Vomiting grade 2+(during RT)	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
11.1 Mesalazine	2	144	Risk Ratio (IV, Random, 95% CI)	0.73 [0.43, 1.25]
11.2 Olsalazine	1	58	Risk Ratio (IV, Random, 95% CI)	2.18 [0.62, 7.61]
12 Medication for GI symptom control	2	156	Risk Ratio (IV, Random, 95% CI)	1.91 [1.26, 2.90]
12.1 Mesalazine	1	72	Risk Ratio (IV, Random, 95% CI)	2.12 [1.15, 3.91]
12.2 Sulfasalazine	1	84	Risk Ratio (IV, Random, 95% CI)	1.75 [0.99, 3.08]
13 Discontinuation of study medication	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
13.1 Sulfasalazine	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 10. Corticosteroids vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Late GI toxicity: grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Late GI toxicity: grade 1+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Diarrhoea: grade 2+ (up to 12 months)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Rectal bleeding (up to 12 months, ungraded)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Faecal urgency (up to 12 months, ungraded)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 11. Superoxide dismutase vs no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+ (3 months)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Late GI toxicity: grade 2+ (1 year)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Late GI toxicity: grade 2+ (2 years)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 12. Amifostine vs no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+ (during RT)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Amifostine vs no treatment	3	278	Risk Ratio (IV, Random, 95% CI)	0.25 [0.15, 0.42]
1.2 Rectal amifostine vs SC amifostine	1	53	Risk Ratio (IV, Random, 95% CI)	0.32 [0.01, 7.55]
2 Acute GI toxicity: grade 2+(up to 3 months)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Acute GI toxicity: grade 1+(up to 3 months)	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1 Amifostine vs no treatment	1	44	Risk Ratio (IV, Random, 95% CI)	0.12 [0.01, 2.12]
3.2 Rectal amifostine vs SC amifostine	1	53	Risk Ratio (IV, Random, 95% CI)	0.26 [0.08, 0.84]

4 Late GI toxicity: grade 2+	2	249	Risk Ratio (IV, Random, 95% CI)	1.48 [0.64, 3.45]
5 Late GI toxicity: grade 1+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Diarrhoea grade 2+ (during treatment)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Discontinuation of RT	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 13. Bile acid sequestrants vs no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 GI symptom scores	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Acute GI toxicity: grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Diarrhoea: grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Medication for symptom control	2	64	Risk Ratio (IV, Random, 95% CI)	2.49 [0.29, 21.34]

Comparison 14. Magnesium oxide vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Medication for symptom control	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Discontinuation of study medication	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 15. Misoprostol vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Diarrhoea grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Diarrhoea grade 2+ (1+ years post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Rectal bleeding grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Rectal bleeding grade 2+ (1+ years post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Tenesmus 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Tenesmus 2+ (1+ years post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

8 Faecal urgency 2+ (during RT)	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
9 Faecal incontinence (1+ years post-RT)	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
10 Pain/cramps 2+ (during RT)	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 16. Octreotide vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea grade 2+ (acute)	2	340	Risk Ratio (IV, Random, 95% CI)	1.01 [0.76, 1.35]
2 Rectal bleeding grade 2+ (acute)	2	340	Risk Ratio (IV, Random, 95% CI)	1.65 [1.21, 2.24]
3 Tenesmus grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Vomiting grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Pain/cramps grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Faecal incontinence grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Medication for GI symptom control	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8 Discontinuation of study medication	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 17. Selenium vs no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea grade 2+ (acute)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 18. Sodium butyrate enema vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Acute GI toxicity grade 1+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 19. Sucralfate vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+ (during RT)	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Oral	1	335	Risk Ratio (IV, Random, 95% CI)	1.07 [0.83, 1.39]
1.2 Rectal	1	126	Risk Ratio (IV, Random, 95% CI)	1.18 [0.87, 1.60]
2 Acute GI toxicity: grade 1+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.1 Oral	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Late GI toxicity: grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3.1 Oral	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Diarrhoea grade 2+ (during RT)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1 Oral	4	284	Risk Ratio (IV, Random, 95% CI)	0.81 [0.41, 1.62]
4.2 Rectal	1	83	Risk Ratio (IV, Random, 95% CI)	0.82 [0.44, 1.53]
5 Rectal bleeding grade 2+(during RT)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1 Oral	4	604	Risk Ratio (IV, Random, 95% CI)	1.32 [1.10, 1.60]
5.2 Rectal	1	83	Risk Ratio (IV, Random, 95% CI)	0.87 [0.61, 1.24]
6 Pain/cramps grade 2+(during RT)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.1 Oral	3	269	Risk Ratio (IV, Random, 95% CI)	0.97 [0.58, 1.60]
6.2 Rectal	1	83	Risk Ratio (IV, Random, 95% CI)	1.02 [0.15, 6.93]
7 Faecal urgency grade 2+ (during RT)	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7.1 Oral	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Rectal	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Faecal incontinence grade 2+ (during RT)	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8.1 Oral	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Rectal	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9 Tenesmus grade 2+(during RT)	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected
9.1 Oral	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Rectal	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10 Medication for symptom control	4	313	Risk Ratio (IV, Random, 95% CI)	0.84 [0.49, 1.42]
10.1 Oral	4	313	Risk Ratio (IV, Random, 95% CI)	0.84 [0.49, 1.42]
11 Discontinuation of study medication	4	348	Risk Ratio (IV, Random, 95% CI)	1.02 [0.48, 2.18]
11.1 Oral	4	348	Risk Ratio (IV, Random, 95% CI)	1.02 [0.48, 2.18]

Comparison 20. Diet vs control (usual on-treatment diet)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+ (during RT)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Low-fat diet	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Acute GI toxicity: grade 1+ (during RT)	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.1 Lactose-restricted diet	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Low-fibre diet	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Low-fat diet	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Late GI toxicity: grade 1+	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Lactose-restricted diet	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Low-fibre diet	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Diarrhoea grade 1+ (during RT)	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1 Lactose-restricted diet	1	119	Risk Ratio (IV, Random, 95% CI)	0.74 [0.45, 1.23]
4.2 High-fibre diet	2	74	Risk Ratio (IV, Random, 95% CI)	1.0 [0.94, 1.07]
4.3 Low-fibre diet	1	119	Risk Ratio (IV, Random, 95% CI)	0.74 [0.45, 1.23]
5 Diarrhoea grade 2+ (during RT)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1 Elemental diet	1	50	Risk Ratio (IV, Random, 95% CI)	0.79 [0.45, 1.38]
5.2 Low-fat	1	76	Risk Ratio (IV, Random, 95% CI)	0.61 [0.33, 1.13]
5.3 High-fibre diet	2	74	Risk Ratio (IV, Random, 95% CI)	0.65 [0.38, 1.10]
6 GI symptom score (during RT)	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Low-fat diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Elemental diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 High-fibre diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.4 Low-fibre diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 GI symptom score (1 year after RT)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 High-fibre diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Low-fibre diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 GI symptom score - mean change from baseline (at end of RT)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8.1 High-fibre diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Low-fibre diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9 GI symptom score - mean change from baseline (1 year after RT)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.1 High-fibre diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Low-fibre diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10 RT discontinuation	2	187	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.1 High-fibre diet	1	108	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Low-fat diet	1	79	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 QoL (during RT)	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.1 High-fibre diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Low-fibre diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.3 Low-fat diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.4 Elemental diet	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12 QoL (1 year after RT)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

12.1 High-fibre diet	1	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Low-fibre diet	1	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 21. Counselling vs no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 GI symptom score (acute)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Diarrhoea: grade 2+ (end of RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Diarrhoea grade 2+ (3 months post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Diarrhoea grade 2+ (5 years post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Weight loss: grade 2+ (end of RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Weight loss: grade 2+ (3 months post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Vomiting: grade 2+ (end of RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8 Vomiting: grade 2+ (3 months post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
9 Medication for symptom control (end of RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
10 Medication for symptom control (3 months post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
11 QOL	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.1 Fatigue (5-point VAS)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Sleeping problem (5-point VAS)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 22. Protein supplement vs no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea: grade 2+ (end of RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Diarrhoea grade 2+ (3 months post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Diarrhoea grade 2+ (5 years post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Vomiting: grade 2+ (end of RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Vomiting: grade 2+ (3 months post-RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Weight loss: grade 2+ (end of RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

7 Weight loss: grade 2+ (3 months post-RT)	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
8 Medication for symptom control (end of RT)	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
9 Medication for symptom control (3 months post-RT)	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 23. Glutamine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Acute GI toxicity: grade 1+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Late GI toxicity: grade 2+ (1 year)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Late GI toxicity: grade 1+ (1 year)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Diarrhoea grade 2+(during RT)	4	287	Risk Ratio (IV, Random, 95% CI)	0.98 [0.78, 1.24]
6 Tenesmus grade 2+(during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Pain/cramps grade 2+(during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8 Rectal bleeding grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
9 Vomiting grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
10 Nausea grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
11 Medication for GI symptom control	2	198	Risk Ratio (IV, Random, 95% CI)	2.82 [1.05, 7.58]
12 Faecal incontinence (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
13 Faecal incontinence (1 year post RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
14 Faecal incontinence (2 year post RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
15 Pain/cramps grade 2+(during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
16 Pain/cramps grade 2+(1 year post RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
17 Pain/cramps grade 2+(2 year post RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
18 Rectal bleeding grade 2+ (1 year post RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
19 Rectal bleeding grade 2+ (2 year post RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Comparison 24. Probiotics vs control (placebo or no intervention)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea: grade 2+ (during RT)	5	923	Risk Ratio (IV, Random, 95% CI)	0.43 [0.22, 0.82]
2 Weight loss grade 2+	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Medication for GI symptom control	6	507	Risk Ratio (IV, Random, 95% CI)	0.53 [0.32, 0.88]

Comparison 25. Proteolytic enzymes vs control (placebo or no intervention)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute GI toxicity: grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Acute GI toxicity: grade 1+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Diarrhoea: grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Vomiting grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Rectal bleeding grade 2+ (during RT)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Medication for GI symptom control	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

ADDITIONAL TABLES

Table 1. Toxicity scoring systems

Common gastrointestinal toxicity scoring systems				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
EORTC/RTOG small/ large intestine: acute morbidity	Increased frequency or change in quality of bowel habits not requiring medication / rectal discomfort not requiring analgesics	Diarrhoea requiring medication / mucous discharge not necessitating sanitary pads / rectal or abdominal pain requiring analgesics	Diarrhoea requiring parenteral support / severe mucous or blood discharge necessitating sanitary pads / abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion

Table 1. Toxicity scoring systems (*Continued*)

EORTC/ RTOG small/large intestine: late morbidity	- Mild diarrhoea - Mild cramping - Bowel movement 5 times daily - Slight rectal discharge or bleeding	- Moderate diarrhoea and colic - Bowel movement > 5 times daily - Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis / Perforation Fistula
CTCAE version 4.0 (diarrhoea)	Increase of < 4 stools a day over baseline	Increase of 4 - 6 stools per day over baseline	Increase of ≥ 7 stools a day over baseline; incontinence; hospitalisation indicated	Life-threatening consequences; urgent intervention indicated
CTCAE version 4.0 (rectal bleeding)	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterisation indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated

Grade 0 = no symptoms; Grade 5 = death. Toxicity grade should reflect the most severe symptoms occurring during a period of evaluation.

Abbreviations: EORTC = European Organisation for Research and Treatment of Cancer; RTOG = Radiation Treatment Oncology Group; CTCAE = Common Terminology Criteria for Adverse Events

For more details, refer to www.rtog.org/ResearchAssociates/AdverseEventReporting/ (accessed 03/02/2017) and Cox 1995.

Table 2. Summary table of single study interventions with limited data*

Study ID	Intervention (I)	Comparator (C)	Participants	Cancer type	Primary or adjuvant radiotherapy	Findings		Risk of bias judgement (study limitations)	Study conclusions	Reviewer comments
						Acute gastrointestinal toxicity	Late gastrointestinal toxicity			
Pharmacological interventions										
Hombrink 2000	smectite	placebo	176 men and women	mainly pelvic, plus some abdominal cancers	primary and adjuvant	NR Reported time to development of diarrhoea	NR	Unclear risk	"Prophylactic smectite can delay the development of RT-induced diarrhoea. A statistical signif-	No usable data for review purposes

Table 2. Summary table of single study interventions with limited data* (*Continued*)

									icance could not be verified..."	
Kardamakis 1995	tropisetron (oral)	placebo	33 men and women	various pelvic	primary	5/? vs 4/? No difference in number of bowel actions	NR	High risk	Tropisetron showed no antidiarrhoeal effect	Poorly-reported study that suggests no benefit
McGuffin 2016	simethicone (oral)	placebo	78 men	prostate	primary	NR	NR	Unclear risk	"standardized bowel preparation education alone may be sufficient to limit the variation in rectal size over a course of radiation treatment."	GI toxicity was not reported by study arm in this conference abstract, but authors noted no benefits with this antiflatulence treatment
Razzaghdoust 2014	famotidine (oral)	placebo	36 men	prostate	primary	G2+ GI toxicity 2/16 (I) and 10/18 (C)	NR	Unclear risk	"We demonstrated that famotidine significantly reduces radiation-induced injury on rectal mucosa..." Famo-	Pilot study - more research needed

Table 2. Summary table of single study interventions with limited data* (*Continued*)

									tidine inhibits gastric acid secretion and is a powerful free radical scavenger	
Stryker 1979	ibuprofen (oral)	no intervention	31 women/1 man	gynaecological/ prostate	primary	NR Reported no. of participants reporting 4 or more stools a day at least once: 10/17 (I) vs 8/15 (C) Vomiting: 0/17 (I) vs 4/15 (C)	NR	High risk	"The incidence and severity of diarrhoea was the same." "Prophylactic ibuprofen may be beneficial in reducing the severity of nausea and preventing radiation-induced vomiting..."	Older study with very uncertain evidence and applicability
Non-pharmacological interventions										
Ahmad 2010	soy diet	regular diet	42 men (26 analysed)	prostate	primary	cramping or diarrhoea: 2/13 (I) vs 1/13 (C) pain with bowel movements: 1/	cramping or diarrhoea: 1/13 (I) vs 3/13 (C) pain with bowel movements: 1/	High risk	Soy isoflavones might reduce GI and other radiation-induced toxicity	High attrition was a problem in this underpowered study, so findings are inconclusive/

Table 2. Summary table of single study interventions with limited data* (*Continued*)

						13 (I) vs 0/13 (C)	13 (I) vs 2/13 (C)			very uncertain
Arregui Lopez 2012	steady diet	control (exclusion diet)	29	rectal	primary	NR	NR	High risk	"control group showed a significant increase in incidence and grade of acute diarrhoea > G2 at end of treatment"	Available as abstract only with scant details of the intervention and data
Emami 2014	green tea (oral tablet)	placebo	23 men and 19 women	various pelvic	primary and adjuvant	G1+ diarrhoea: 7/21 (I) vs 12/21 (C)	NR	High risk	"Green tea. ..could be effective in decreasing the frequency and severity of radiotherapy induced diarrhoea"	Underpowered study, so findings are inconclusive/ very uncertain - more research needed
Hejazi 2013	curcumin (oral tablet)	placebo	40 men	prostate	primary	Mean GI symptom score: 25 (12.4) (I) vs 20.0 (18.0) (C)	NR	High risk	Curcumin "could not reduce the severity of bowel symptoms" but "could confer radioprotective effect... through	Underpowered study, so findings are inconclusive/ very uncertain - more research needed

Table 2. Summary table of single study interventions with limited data* (*Continued*)

									reducing severity of radiotherapy related urinary symptoms"	
Other aspects of radiotherapy delivery										
Gaya 2013	belly board	standard practice	30	rectal	NR	Poorly-reported toxicity data could not be extracted according to treatment arms	NR	High risk	"Set-up reproducibility, small bowel V15, patient comfort and satisfaction were all significantly improved by the use of the Belly Board"	Interim analysis with serious design limitations
Habl 2016	proton technique	carbon ion technique	92 men	prostate	primary	G2+ diarrhoea occurred in 4/46 (I) vs 0/45 (C) participants, respectively. 2 participants in the proton arm developed G3 rectal fistulas	NR	Unclear risk	Authors attributed the fistulas to the use of spacer gel, which they have stopped using. Diarrhoea scores and bowel	More evidence is needed

Table 2. Summary table of single study interventions with limited data* (*Continued*)

									symptoms tended to be worse in the proton arm than the carbon ion arm at end of treatment, 6 weeks and 6-month assessments. Authors concluded that hypofractionation with "either carbon ions or protons results in comparable acute toxicities and QoL parameters."	
Ljubenkov 2002	patient table	standard practice	183 women	cervix	NR	G2+ "stool frequency" during RT occurred in 7/90 (I) and 34/93 (C) participants; 8/90 (I)	NR	High risk	"Use of the unique patient-table led to protection of the small bowel during radio-	Serious study design limitations undermine the usefulness of these findings

Table 2. Summary table of single study interventions with limited data* (*Continued*)

						vs 39/93 (C) required anti-diarrhoeal medication; G2+ cramping occurred in 4/90 (I) vs 32/93 (C)			therapy for uterine malignancies... "	
Sidik 2007	HBOT**	no HBOT	65 women	cervix	NR	Change from baseline in LENT-SOMA scores were reported but data were not usable (reported as percentages)	Change from baseline in LENT-SOMA scores were reported but data were not usable (reported as percentages)	High risk	"The HBOT procedure yield hyperoxia, hypervascular and hypercellular that improved the tissue damage after pelvic radiation. This condition will decrease acute and late side effect showed by LENT SOMA scale and improved QoL shown by Karnofsky score. "	Serious study design limitations undermine the usefulness of these findings

* For more details, please see individual Characteristics of Studies tables in Characteristics of included studies.

**Details of the timing of this intervention were sparse; however, it appeared that HBOT in this study was administered to women after they had completed their course of pelvic RT.

Abbreviations: C = control; HBOT = hyperbaric oxygen therapy; I = intervention; NR = not reported

CONTRIBUTIONS OF AUTHORS

Theresa Lawrie: study selection, data extraction, data entry, analysis and interpretation of evidence, writing the review;

John Green: study selection, data extraction, data entry and interpretation of evidence, writing the review;

Mark Beresford: data extraction, data entry, resolving queries, interpretation of evidence;

Linda Wedlake: data extraction, data entry, interpretation of evidence;

Sorrel Burden: data extraction, interpretation of evidence;

Susan Davidson: data extraction, interpretation, resolving queries;

Simon Lal: interpretation of evidence;

Caroline Henson: interpretation of evidence;

Jervoise Andreyev: resolving queries, interpretation of evidence.

Theresa Lawrie wrote the first draft of the review with contributions from the other authors. All authors advised on and approved the final version of the review.

DECLARATIONS OF INTEREST

Theresa Lawrie: none declared

Mark Beresford: none declared

John Green: none declared

Linda Wedlake: none declared

Sorrel Burden: none declared

Simon Lal: none declared

Susan Davidson: none declared

Caroline Henson: none declared

Jervoise Andreyev: none declared

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of participants *section:* Our protocol stated that we would attempt to contact authors of studies that included a mixed participant population. Given the scope and timeline of this review, the often lengthy period since publication of the studies, and resources, we found that this was not practical or feasible. After initial efforts to contact authors for this purpose and for missing data, and following a poor response, we had to abandon attempts at sourcing unpublished data.

Types of outcome measures*section:* We modified the outcome 'mild GI symptoms (grade 1 toxicity)' to 'GI toxicity grade 1+'. We added the following sentence to this section "We excluded studies that evaluated dosimetric parameters only." because dosimetric parameters (e.g. total bowel dose) are weak proxy outcomes, for which the relationship with symptoms of GI toxicity is unclear. We considered that studies evaluating only these types of outcomes would add little to the overall conclusions of the review, but could increase the workload substantially.