Clinical Oncology 36 (2024) 318–334

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Interventions for Managing Late Gastrointestinal Symptoms Following Pelvic Radiotherapy: a Systematic Review and Meta-analysis

H. Berntsson *, A. Thien †, D. Hind *, L. Stewart ‡, M. Mahzabin ‡, W.S. Tung ‡, M. Bradburn *, M. Kurien ‡

* Sheffield Centre for Health and Related Research, University of Sheffield, Sheffield, UK
† Department of General Surgery, Raja Isteri Pengiran Anak Saleha Hospital, Bandar Seri Begawan, Brunei
‡ The Medical School, University of Sheffield, Sheffield, UK

Abstract

Aims: Pelvic radiotherapy can induce gastrointestinal injury and symptoms, which can affect quality of life. We assessed interventions for managing these symptoms.

Materials and methods: A review of randomised controlled trials published between January 1990 and June 2023 from databases including MEDLINE, EMBASE, CENTRAL, CINAHL, clinicaltrials.gov, ISRCTN and grey literature sources was conducted. Meta-analyses were carried out using the DerSimonian and Laird random effects model to produce overall treatment differences with 95% confidence intervals.

Results: Twenty-eight studies (2392 participants) of varying methodological quality were included. 4% formalin was superior to sucralfate for improving gastrointestinal symptom score (standardised mean difference [SMD] −1.07, 95% confidence interval −1.48 to −0.65). Argon plasma coagulation (APC) was inferior to sucralfate (SMD 1.22, 95% confidence interval 0.84 to 1.59). Counselling positively influenced symptom score (SMD −0.53, 95% confidence interval −0.76 to −0.29), whereas hyperbaric oxygen therapy showed conflicting results. Sucralfate combined with APC increased endoscopic markers of moderate–severe bleeding versus APC alone (risk ratio 2.26, 95% confidence interval 1.12 to 4.55). No definite conclusions on pain, incontinence, diarrhoea, tenesmus or quality of life interventions were confirmed.

Conclusions: Small study sizes, methodological quality and heterogeneity limit support of any individual intervention. APC and 4% formalin seem to be promising interventions, with further larger randomised controlled trials now warranted.

Key words: Diarrhoea; gastrointestinal symptoms; pelvic radiotherapy; rectal bleeding

Introduction

Radiation therapy is an established part of multimodal treatment for gastrointestinal, genitourinary and gynaecology malignancy. Radiation doses to pelvic cancers, including the rectum, prostate and cervix, can total up to 90 Gy depending on cancer stage and treatment strategy [1]. This may be via external beam radiation therapy, where a radiation beam is delivered from outside the body to the target tumour through beam arrays using linear accelerators. Brachytherapy is an alternative and internal form of radiation therapy, where the radiation sources are implanted within, or in close proximity to, the target tumour.

Invariably, non-targeted tissues suffer collateral damage, especially the rectum and sigmoid colon [2]. An estimated 1.5–2 million cancer survivors suffer from radiation-induced gastrointestinal effects [3]. Symptoms can be acute, up to 3 months after radiation, or chronic, those persisting beyond 3 months [3]. The reported incidence of chronic toxicity is estimated as 20–30%, but may be underestimated due to variability in definition and reporting [4], and may be growing in prevalence as cancer survivorship improves. Chronic gastrointestinal symptoms can include bleeding and proctopathy symptoms (urgency, tenesmus, diarrhoea, faecal incontinence, mucus discharge). Bowel habit is permanently changed in

Author for correspondence: H. Berntsson, Sheffield Centre for Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK.
E-mail address: h.berntsson@sheffield.ac.uk (H. Berntsson).

https://doi.org/10.1016/j.clon.2024.02.011

90%, quality of life reduced in 50% and moderate to severe disabling effects experienced in 20–40% of patients [5], resulting in a substantial humanistic and economic burden [6]. The pathological mechanisms leading to gastrointestinal toxicity are variable and influenced by epithelial cell damage, vascular damage, inflammation cytokine release and altered microbial composition [7].

Clinical practice guidelines recommend stepwise escalation from medical to endoscopic and surgical methods, depending on symptom severity and health system resources [8–10]. However, published systematic reviews do not cover all treatment options and are currently out of date [11]. We conducted this systemic review to identify and evaluate the effectiveness of interventions for the management of late gastrointestinal symptoms following pelvic radiotherapy.

Materials and Methods

This systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and registered on PROSPERO before study selection.

Eligibility Criteria

Randomised controlled trials (RCTs) were eligible for inclusion if they involved adult cancer patients who developed chronic gastrointestinal symptoms 3 months or more after pelvic radiotherapy, or progressed from acute radiation proctitis. Eligible studies evaluated medical therapies – antibiotics, 5-aminosalicylic acid (5-ASA) derivatives, short chain fatty acid (SCFA) preparations, sucralfate preparations, corticosteroids, probiotics, antioxidants, pentoxifylline and micronised purified flavonoid fraction (MPFF); endoscopic interventions – argon plasma coagulation (APC), bipolar cautery or heater probe coagulation, radiofrequency ablation (RFA), formalin applications and Hemospray®; or non-pharmaceutical therapies – hyperbaric oxygen therapy (HBOT) and counselling. No restriction was placed on comparators, but trials had to report at least one outcome of interest (see below). Non-randomised studies were excluded.

Search Strategy

We combined thesaurus and free text terms (see Supplementary Material) to search MEDLINE, EMBASE, CINAHL (via Ovid), Web of Science and CENTRAL (via the Cochrane Library) for papers published in English from January 1990 to June 2023. We hand-searched the reference lists of full-text articles.

Study Selection

Three review authors independently screened titles and abstracts and potentially eligible full texts against the eligibility criteria. Disagreements were resolved through discussion with senior members of the review team.

Data Extraction

Three review authors extracted data on characteristics of studies (country, inclusion criteria), participants (age, sex, type and location of cancer, stage of cancer), interventions characteristics (dose and duration of radiotherapy, character of comparators) and outcome measures (see below) into a spreadsheet. A second reviewer checked the accuracy of data extraction on all included studies.

Risk of Bias

Three authors assessed the study risk-of-bias using the Cochrane Risk of Bias 2 (RoB2) tool [12–14], with discrepancies resolved by senior members of the review team. Following the comprehensive guidance and signalling questions [15], domains were graded as ‘low’, ‘some concerns’ or ‘high’ risk, with domain gradings informing an assessment of overall study risk-of-bias.

Effect Measures

Primary outcomes were structured survey instruments measuring gastrointestinal symptom scores or health-related quality of life (HRQoL) and gastrointestinal toxicity symptoms (per rectal bleeding, abdominal cramps/pain, faecal incontinence, diarrhoea and tenesmus). Where instruments were judged to assess the same outcome measure, which was expressed in the same way (i.e. continuous or categorial data), then a meta-analysis was conducted.

Data Synthesis and Analysis

Where possible we calculated mean differences and confidence intervals for continuous outcomes. As continuous outcomes – gastrointestinal symptom and HRQoL scores – typically involved the use of different instruments, we also used calculated standardised mean differences (SMDs) to present findings on a uniform scale of standard deviation units. Dichotomous data for gastrointestinal toxicity symptoms were presented as risk ratios with 95% confidence intervals. Where necessary, we transformed published standard errors, confidence intervals or *P*-values into standard deviations using the RevMan Calculator [16]. Where studies reported medians and interquartile ranges, these were transformed to means and standard deviations using a hierarchy of methods, the order of preference being: the McGrath Box Cox [17], McGrath quartile estimate [17], Hozo [18] and Wan [19] methods. We used RevMan 5 [20] and the DerSimonian and Laird inverse variance random effects model [21] to meta-analyse trial results. We assessed heterogeneity using the I^2 statistic. The GRADEpro approach was used to check the quality of evidence for studies reporting gastrointestinal symptom scores [22,23].

Results

Study Selection

Excluding duplicates, 6170 records were identified by the searches and screened (Figure 1). Three potentially relevant full-text reports could not be retrieved [24–26] and three potentially eligible RCTs were ongoing [27–29]; the full texts of 132 were screened and a further 104 were excluded. Twenty-eight studies from 16 countries, published between 1991 and 2022 were included (Table 1) with a total of 2392 participants. The median number of participants per trial was 61 (range 7–246).

Population Characteristics

The mean age of participants ranged from 44.7 [30] to 78 [31] years old (median 62.2 years). The location of cancers included the cervix (n = 18) [12,30–46], prostate (n = 19) [12–14,31,32,34–36,38,39,41,43–45,47–51] and anus/rectum (n = 6) [31,32,36,38,43,45]; location was unspecified in four cases [46,52–54]. Eleven studies reported radiation dosage (mixed external beam radiotherapy and brachytherapy); none involved dosages below 45 Gy, but two (brachytherapy studies) used dosages of over 70 Gy [31,51]. The length of follow-up ranged from 4 weeks [39] to 5 years [53].

Intervention Characteristics

Ten studies evaluated endoscopic interventions: APC (n = 1) [45], bipolar electrocoagulation or heater probe electrocoagulation (n = 2) [12,35], RFA (n = 1) [46], formalin (n = 6) [34,37,40–42,55] and Hemospray® (n = 1) [49]. Fifteen studies evaluated pharmaceutical interventions: antibiotics (n = 3) [13,41,42], 5-ASA derivatives (n = 2)

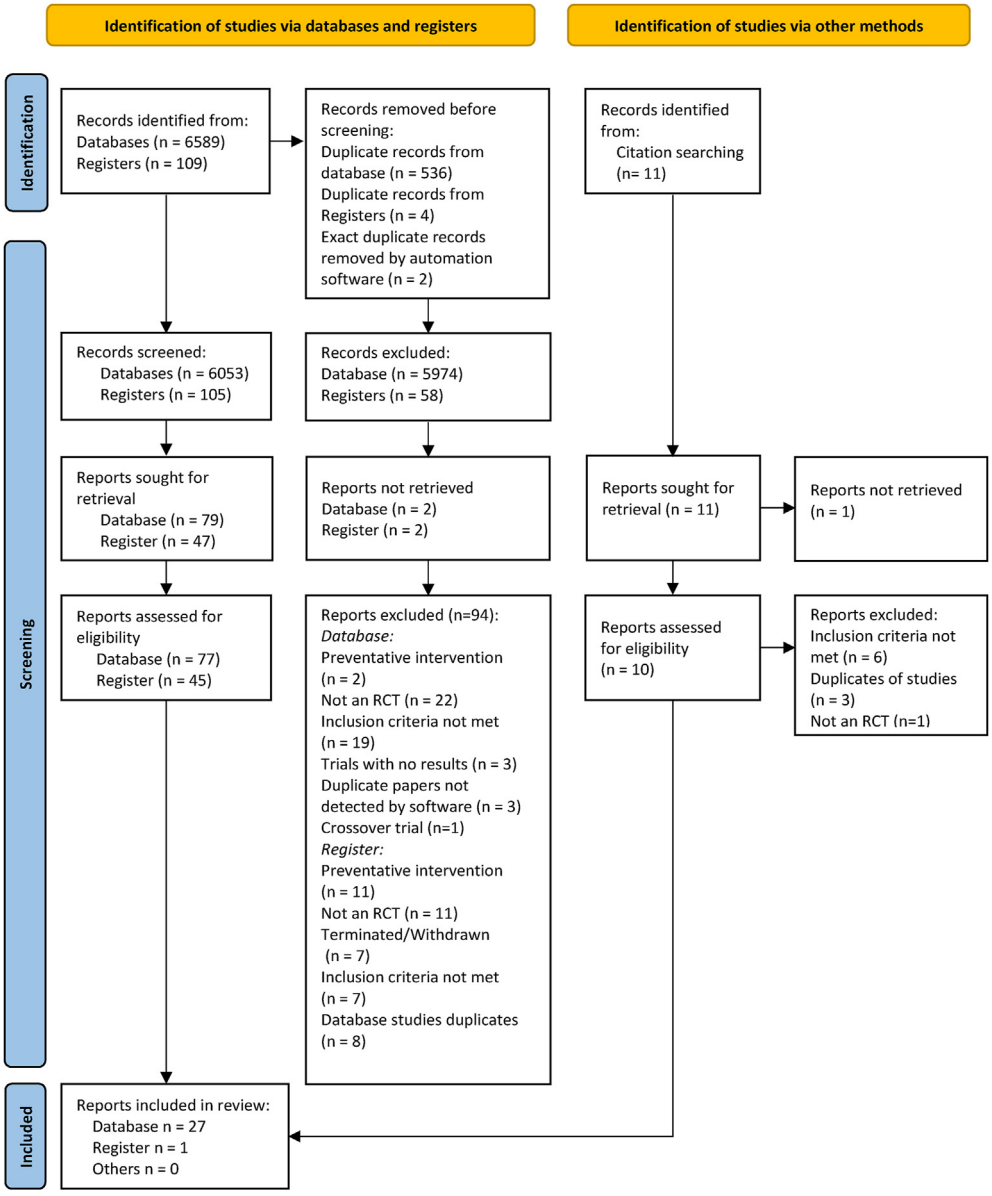

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table 1
Study characteristics

Study	Year	Country	Method	Sample size	Study duration	Population	Intervention	Comparator (s)	Outcomes
Kochhar [39]	1991	India	Double-blind RCT	37	4 weeks	Radiation-induced proctosigmoiditis confirmed on symptoms (diarrhoea, bleeding, tenesmus) and endoscopic grading	Sulfasalazine 1 g TDS + prednisolone retention enema 20 mg BD	Placebo 2 tablets TDS + sucralfate retention enema 2 g BD	Clinical or endoscopy improvement in disease grading using the sign test
Henriksson [50]	1995	Sweden	Double-blind RCT	40	5 weeks	Chronic bowel discomfort 1 year after radiation therapy	Verum hälsofil 300 ml BD	Norrlands fil 300 ml BD	Daily self-recording of bowel action (frequency, stool consistency, pain, occurrence of blood or mucus) and other medications used Stool samples analysed before and after 5-week treatment period
Jensen [12]	1997	America	RCT	21	Not reported	Chronic recurrent haematochezia and anaemia Completed radiotherapy >24 months prior treatment Failed medical treatment	Bipolar probe 50W BICAP generator (10–15 W and 1 s pulses)	Heater probe Olympus 10–15 J	Sigmoidoscopies 4–6 weekly till bleeding stopped and all telangiectasias obliterated Examined every 4–6 months
Pinto [54]	1999	Portugal	Double-blind RCT	19	2 years	Clinical and histological Dx chronic radiation proctitis Rectal bleeding Need for transfusion or haemoglobin < 6	Short chain fatty acid enemas (sodium acetate 60 mM, sodium propionate 30 mM, sodium butyrate 40 mM) Enemas 60 ml BD for 5 weeks	Placebo saline isotonic enemas 60 ml BD for 5 weeks	Number of days with rectal bleeding. Haemoglobin measurement Endoscopic score
Cavcić [13]	2000	Croatia	Quasi-randomised	60	10 years	Chronic symptoms (bleeding and diarrhoea)	Metronidazole 400 mg TDS PO, mesalazine 1 g TDS PO and betamethasone enema OD PR for 4 weeks	Mesalazine 1 g TDS PO and betamethasone enema OD PR for 4 weeks	Self-recorded details of bowel action (number of movements, amount and frequency of bleeding) and other medication usage Objective scoring (rectal and diarrhoea) of patient response

(*continued on next page*)

Table 1 (*continued*)

Study	Year	Country	Method	Sample size	Study duration	Population	Intervention	Comparator (s)	Outcomes
Ehrenpries [14]	2005	America	Double-blind RCT	19	Not reported	Chronic radiation proctopathy (diarrhoea, rectal urgency, rectal pain, tenesmus, rectal bleeding, faecal incontinence) Completed radiation therapy >6 months prior RPSAS - two symptoms with score 3 on weekly basis	Retinol palmitate 10 000 IU in capsules	Placebo capsules	Reduction of at least two symptoms by at least 2 points Comparison of total RPSAS score after 30 days or 90 days
Sidik [30]	2007	Indonesia	Open randomised parallel prospective	65	19 months	Cervical cancer patients who had received radiation therapy	Hyperbaric oxygen therapy	Control	Karnofsky score (QoL) and LENT-SOMA score (symptom score) at baseline, after hyperbaric oxygen therapy and at 6 months
Venkitaraman [47]	2008	England	Non-blind RCT	50	9 years	Prostate cancer Symptomatic rectal bleeding >6 months since pelvic radiation therapy No disease progression Life expectancy >6 months Received standard treatment and endoscopic cautery	Standard therapies + oral pentoxifylline 400 mg TDS for 6 months	Standard therapies	Self-recorded frequency and severity of rectal bleeding
Clarke [53]	2008	Australia, America	Multicentre RCT double-blind crossover	120	Unclear	Rectal late radiation tissue injury ≥3 months, non-responder to other therapies	Hyperbaric oxygen therapy (100% 2 ATA oxygen) 90 min, OD, 5 × weekly, 30 treatments 10 additional treatments provided, depending on individual responses	Sham (21% 1.1 ATA oxygen, OD, 5 × a week), 30 treatments 10 additional treatments provided, depending on individual responses	Change in LENT-SOMA score (primary) Expanded Prostate Cancer Index Composite QoL Instrument (secondary)

Table 1 (*continued*)

Study	Year	Country	Method	Sample size	Study duration	Population	Intervention	Comparator (s)	Outcomes
Germain [36]	2011	Canada	Phase III RCT	246	5 years	Rectal, cervical, endometrial or prostatic cancer Surgery then radiation therapy or chemotherapy Diarrhoea	Bifilact *Lactobacillus acidophillis* + *Bifidobacterium longum* (standard 2 caps of 1.3 milliards) OR 3 caps of 10 milliards	Placebo	Digestive symptoms noted, analysis of time of appearance of diarrhoea Time of appearance and grade of diarrhoea
Lenz [35]	2011	Brazil England	RCT	30	4 years	Rectal bleeding 6 months after radiation therapy, endoscopically confirmed telangiectasia (previous medical therapy 5 BEC, 4 APC)	BEC 50 W Light direct pressure	APC (40 W 1 l/min gas flow) No direct contact	The severity of CRCP was endoscopically and clinically evaluated using telangiectasia distribution, involved surface area, and presence of fresh blood Saunders score (success = eradication, failure = >7 sessions or other treatment)
Oliner [46]	2012	America	RCT	7	Not reported	Chronic radiation proctitis 90 days from end of radiation therapy	Radiofrequency energy	APC	Proctitis was scored based on RTOG Vienna endoscope scoring system Primary reduction or absence of bleeding not needing further treatment after 6 months Secondary time to resolution of symptoms, need for blood transfusion
Nelamangala Ramakrishnaiah [40]	2012	India	RCT	102	22 months	Rectal bleeding from chronic haemorrhagic radiation proctopathy following radiation therapy and symptoms according to RPSAS	Formalin (4%) dab gauze applied for 2 min until mucosa turned pale Perianal skin zinc oxide cream	Sucralfate 1 g in 100 ml NS and 100 mg prednisolone enema, BD for 7 −10 days	Symptoms of radiation proctitis graded by RPSAS and simodoscopic grade before and 4 weeks after prescribed

(*continued on next page*)

Table 1 (*continued*)

Study	Year	Country	Method	Sample size	Study duration	Population	Intervention	Comparator (s)	Outcomes
Sahakitrungruang [41]	2012	Thailand	RCT	50	16 months	Symptomatic haemorrhagic radiation proctopathy >6 months without complications of stricture, ulceration, fistula and sepsis	Daily self-administration low gravitational force (1 m high) colonic irrigation of 1 l tap water via 20F Foley catheter + ciprofloxacin 500 mg BD + metronidazole 500 mg TDS for 1 week	4% formalin-soaked gauze for 3 min direct application using proctoscopy then immediate cleansing with water irrigation	Outcomes after 8 weeks of treatment VRS Haematocrit values No. patients requiring packed red blood cell transfusions Patient survey
Chruscielewska-Kiliszek [43]	2013	Poland	Single-centre double-blind RCT	122	34 months	Chronic radiation proctitis, completed radiation therapy >3/12 months prior, rectal bleeding, radiation-induced telangiectasia	APC + sucralfate 6 g BD daily for 4 weeks APC 1.0, 25–40 W 1 session versus multiple sessions 1–3 days apart APC can be repeated week 8 and 16	APC + placebo tablets for 4 weeks	Disease severity score at 6, 16 and 52 weeks Gilinsky scale for endoscopic severity at week 8 and 16 Haemoglobin, serum iron and serum creatinine levels at weeks 8 and 16 Complications
Andreyev [31]	2013	England	Single-centre prospective three-arm non-blinded RCT	218	6 years (suspension of 5 months)	Gastrointestinal symptoms started during or after radiation therapy Completed radiation therapy at least 6 months before enrolment	Group 1 = Managed according to the algorithm by a consultant gastroenterologist Group 2 = Managed according to the algorithm by a specialist trained nurse	Group 3 = Detailed advice booklet on self-management	IBDQ-B St Marks's faecal incontinence score LENT-SOMA ICSsex ICSmaleSF JensenQ BFLUTSQ HAD, WASA, SF-12 and QALYs
Merino-Rodriguez [44]	2013	Spain	Single-centre RCT	62	4 weeks	Chronic haemorrhagic radiation proctitis APC repeated every 8 weeks if necessary	5-aminosalicylic acid compounds + sucralfate + budesonide + APC	APC only	Comparison of efficacy and safety of regimens using an established scoring technique Before, at week 16 and week 48
Yeoh [48]	2013	Australia	RCT	30	10 years	Intractable rectal bleeding (1 per week or requiring blood transfusion, or both) after radiation therapy (more than 6 months)	APC (IV midazolam, 60–80 W, 2 l argon gas flow)	Topical formalin (GA, gauze pledgets soaked with 4% formalin, 1 min)	LENT-SOMA VAS for bleeding Anorectal function Anal sphincteric morphology

Table 1 (*continued*)

Study	Year	Country	Method	Sample size	Study duration	Population	Intervention	Comparator (s)	Outcomes
Guo [37]	2015	China	Prospective RCT	115	4 years	Chronic haemorrhagic radiation proctitis	10% formalin (gauze soaked in 2 ml) for 2 −3 min until bleeding stopped Oral bisacodyl night before petroleum jelly to perianal skin. End rectum irrigated with NS	4% formalin (gauze soaked in 2 ml)	RPSAS
Singhal [55]	2015	India	RCT	236	3 years	Chronic haemorrhagic radiation proctitis	4% formalin	10% formalin	Symptom Rectoscopy score improvement
Glover [38]	2016	England	Double-blind sham-controlled phase III RCT	84	38 months	Grade 2 gastrointestinal symptoms LENT-SOMA or grade 1 intermittent symptoms for at least 12 months After 3 months of optimum standard treatment including antibiotic treatment, bile acid malabsorption, lifestyle, etc	Hyperbaric oxygen therapy 40 exposures at 2.4 ATA, 100% oxygen at 90 min	Sham 40 exposures at 1.3 ATA 21% oxygen for 90 min	IBDQ and the EORTC QLQ-C30 and QRQ-CR38 at baseline, 2 weeks after treatment end and 3 months, 6 months, 9 months and 12 months after treatment start
Kayal [49]	2018	Canada	RCT	18	28 months	Recurrent rectal bleeding in radiation proctitis	APC + Hemospray	APC	Subjective improvement of rectal bleeding as reported by patient
Sirikurnpiboon [45]	2019	Thailand	Prospective RCT	130	4 years	Radiation proctocolitis from clinic examination with scope and pathology, more than 3 months	Sucralfate suspension 1 g/5 ml using inflation pressure lithotripsy device of 240 ml from rectosigmoid to low rectum	APC 2.3 mm diameter, high frequency unit	Clinical improvement CBC, HCT count Endoscopic findings RTD

(*continued on next page*)

Table 1 (*continued*)

Study	Year	Country	Method	Sample size	Study duration	Population	Intervention	Comparator (s)	Outcomes
Forslund [51]	2020	Sweden	RCT	180	52 months (study period 26 months)		Nutrition intervention (soluble fibre and lactose free) 3 × sessions (baseline, 4 weeks, 8 weeks)	Control habitual diet	EORTC QLQ-C30 (diarrhoea and constipation) GISEQ (patient perceived bother from bowel symptoms) QLQ-PR25 (limitations to daily activities due to bowel symptoms, incontinence, blood, bloated abdomen) HRQoL (global health status, functioning and symptoms) Dietary adherence (FFQ)
Pui [42]	2020	Malaysia	RCT	35	9 months	Haemorrhagic radiation proctitis, at least 1 PR bleed per week	Irrigation self-administered rectal irrigation 1 l clean water via 20F Foley, PO ciprofloxacin 500 mg BD and PO metronidazole 400 mg TDS 1 week	Formalin dab 4% with soaked gauze for 3 min under direct vision using proctoscopy. Flushed with 500 ml water.	VRS
Kronberger [52]	2020	Austria	Multicentre, double-blind RCT	200	1 year	Radiation proctitis with macroscopic bleeding End of radiation therapy ≥3 months to 90 days	Micronised purified flavonoid-fraction 500 mg, 6 tablets 4 days, then 4 tablets 3 days, then 2 tablets 1 year	Placebo	Number of interventions needed to stop acute bleeding by chronic radiation proctitis: surgical, endoscopic or proctoscopic interventions QOL (EORTC QLQ-C30 and QLQ-PRT20) Blood samples - haemoglobin, thrombocytes and coagulation Stool - difference in calprotectin Histological - alterations

Table 1 (*continued*)

Study	Year	Country	Method	Sample size	Study duration	Population	Intervention	Comparator (s)	Outcomes
Furtado [34]	2021	Brazil	RCT	34	24 months	Haemorrhagic radiation proctitis, failed previous conservative treatment	EFI 8Fr spray catheter, 40 ml aliquot formalin 5% sprayed, left for 1 min then aspirated, then another 40 ml aliquot of formalin 5% for 2 min then aspirated. Rinse with 500 ml NS. Repeated every 4 weeks	APC medtronic 25 M 1.5 l/min gas flow, 01–02 mm from mucosa, 4 week basis	VRS Telangiectasia distribution pattern RTOG Modified Radiation Toxicity Scale
Andreyev [32]	2022	UK/USA	Single-centre prospective RCT	62	28 months	Gastrointestinal symptoms of grade 2 or higher in CTCAE v4 or grade 1 with difficult intermittent symptoms, 12 months after radiation therapy	Tocovid SupraBio 200 mg PO BD plus pentoxifylline 400 mg PO BD for 12 months	Placebo	Modified IBDQ EORTC QLQ-C30 and QLQ-CR29 GSRS

ATA, Atmospheres of Absolute Pressure; APC, argon plasma coagulation; BD, Twice Daily; BEC, Bipolar Electrocoagulation; BFLUTSQ, Bristol Female Lower Urinary Tract Symptoms Questionnaire; CBC, complete blood count; CRCP, Chronic radiation coloproctopathy; CTCAE, Common Terminology Criteria for Adverse Events; Dx, diagnosis; EFI, Endorectal Formalin Instillation; EORTC, European Organization for Research and Treatment of Cancer; FFQ, Food Frequency Questionnaire; GA, General Anasthesia; GISEQ, Gastrointestinal Side Effects Questionnaire; GSRS, Gastrointestinal symptom rating scale; HAD, Hospital Anxiety and Depression Scale; HCT, Hematocrit; HRQoL, health-related quality of life; IBDQ, Inflammatory Bowel Disease Questionnaire; ICSmaleSF, The International Continence Society male questionnaire short form; ICSsex, The International Continence Society sex questionnaire; IV, intravenous; JensenQ, JensenQ Questionnaire; LENT-SOMA, Late Effects of Normal Tissues-Subjective, Objective, Management, Analytic; NS, Normal Saline; OD, Once Daily; PO, Oral administration; PR, Rectal administration; QALYs, quality adjusted life years; QoL, quality of life; QLQ-C30, Core Quality of Life Questionnaire; QLQ-CR29, Quality of Life Questionnaire for colorectal cancer; QLQ-PRT20, Quality of Life Questionnaire - Proctitis Module; QLQ-CR38, Quality of Life Questionnaire - Colorectal cancer; RCT, randomised controlled trial; RPSAS, Radiation Proctopathy System Assessment Scale; RTOG, Radiation Therapy Oncology Group; RTD, Rectal Telangiectasia Density; SF-12, Short-form 12 Health Survey Questionnaire; TDS, Three time daily; VAS, Visual Analogue Scale; VRS, Vienna Rectoscopy Score; WASA, Work and Social Adjustment Scale.

[39,44], SCFA ($n = 1$) [54], sucralfate ($n = 4$) [40,43–45], corticosteroids ($n = 2$) [39,44], probiotics/antioxidants ($n = 3$) [14,36,50], pentoxifylline ($n = 2$) [32,47], MPFF ($n = 1$) [52] and medication in addition to APC ($n = 1$) [43]. Five evaluated non-pharmaceutical interventions: HBOT ($n = 3$) [30,38,53] and counselling ($n = 2$) [31,51]. The full intervention characteristics are presented in Table 1.

Risk-of-bias

Study risk-of-bias (Figure 2) was variable. Clearly inappropriate methods were used for sequence generation and allocation concealment in two cases [13,34]. The participants and personnel were not blinded in seven studies [13,31,40,41,48,47,51] and outcome assessment was not blinded in five studies [31,41,47,48,51]. There were clear concerns around incomplete outcome data in three cases [13,30,51] with two of these [30,51] showing differential dropout between arms.

Synthesis

Most findings were limited by small numbers and correspondingly wide confidence intervals. For simplicity, we use the phrase 'did not demonstrate an effect' to describe comparisons whose confidence intervals included the null effect (a zero mean difference or a risk ratio of 1), but these findings should be considered 'equivocal' or 'unproven' rather than as evidence that two therapies are equally effective.

Overall Gastrointestinal Symptom Score

We were able to calculate SMDs for gastrointestinal symptom scores from eight endoscopy trials [34,37,40,42,43,45,46,48], four pharmaceutical trials [14,32,40,43] and four non-pharmaceutical trials [31,38,51,53]. Of the 13 studies included in the meta-analysis, four used robust initial investigations to establish the cause of symptoms and five ruled out some other causes of gastrointestinal symptoms via trial exclusion criteria.

For endoscopic studies (see Supplementary Figures S1 and S2), APC was inferior to sucralfate (one trial; $n = 130$; SMD 1.22, 95% confidence interval 0.84 to 1.59) [45]. No difference was observed when APC was compared with formalin (two trials; $n = 57$; SMD 0.00, 95% confidence interval −0.52 to 0.52, $I^2 = 0\%$) [34,48]. Confidence intervals were not calculable for the small trial comparing APC with RFA (one trial; $n = 7$) [46]. Formalin decreased symptom score compared with sucralfate (one trial; $n = 102$; SMD −1.07, 95% confidence interval −1.48 to −0.65) [40], but not compared with antibiotics (one trial; $n = 34$; SMD −0.27, 95% confidence interval −0.95 to 0.40) [42] or APC (two trials; $n = 57$; SMD 0.00, 95% confidence interval −0.52 to 0.52, $I^2 = 0\%$) [34,48]. Increasing the dose of formalin from the standard 4%–10% did not significantly improve gastrointestinal symptoms (one trial; $n = 115$; SMD 0.28, 95% confidence interval −0.08 to 0.65) [37]. Three trials did not report gastrointestinal symptom scores [12,35,49]. For pharmaceutical trials, one trial (41 participants) showed a SMD in gastrointestinal symptoms of −1.43 (95% confidence interval −2.53 to −0.33), favouring vitamin A over placebo by 1.4 standard deviations [14] (see Supplementary Figure S3). Combination pentoxifylline/vitamin E (one trial; 51 participants; SMD −0.17, 95% confidence interval −0.73 to 0.40) [32] did not significantly improve

Fig 2. Risk of bias of individual studies.

gastrointestinal symptoms compared with placebo. Sucralfate was inferior to endoscopic formalin (one trial; 102 participants; SMD 1.07, 95% confidence interval 0.65 to 1.48) [40]. The addition of medication to APC versus APC plus placebo did not improve the symptom score (one trial; $n = 122$; SMD 0.00, 95% confidence interval −0.35 to 0.35) [43]. One ongoing trial [52] and three published trials [13,39,54] did not report gastrointestinal symptom scores. For non-pharmaceutical trials, the two trials (204 participants) comparing HBOT with placebo reported contradictory findings and the pooled effect should be disregarded due to high heterogeneity (SMD −0.21, 95% confidence interval −0.95 to 0.52, $I^2 = 84\%$) [38,53] (see Supplementary Figure S4). Across two trials (288 participants) counselling reduced gastrointestinal symptoms compared with controls (SMD −0.53, 95% confidence interval −0.76 to −0.29, $I^2 = 0\%$) [31,51] (see Supplementary Figure S5).

Bleeding

Compared with sucralfate, APC did not reduce the number of bleeding episodes (one trial; 130 participants; risk ratio 0.90, 95% confidence interval 0.42 to 1.94) [45] (see Supplementary Figure S6). Sucralfate combined with APC increased endoscopic markers of moderate–severe bleeding compared with APC alone (one trial, 119 participants, risk ratio 2.26, 95% confidence interval 1.12 to 4.55) [43] (see Supplementary Figure S7). Compared with formalin, APC showed no improvement in self-reported bleeding outcomes (one trial; 30 participants; risk ratio 1.00, 95% confidence interval 0.88 to 1.14) [48] or in haemoglobin levels (one trial; 27 participants; risk ratio 1.02, 95% confidence interval 0.68 to 1.53) [34] (see Supplementary Figures S8 and S9). Compared with APC, bipolar electrocoagulation did not improve bleeding (one trial; 29 patients, risk ratio 1.17, 95% confidence interval 0.88 to 1.55) [35] (see Supplementary Figure S10). Compared with APC alone, the addition of Haemospray® did not improve bleeding (one trial; 15 participants; risk ratio 0.93, 95% confidence interval 0.53 to 1.65) [49] (see Supplementary Figure S11). When compared with heater probe electrocoagulation, bipolar electrocoagulation did not reduce bleeding episodes (one study; 21 participants; risk ratio 2.25, 95% confidence interval 0.28 to 18.22) [12] (see Supplementary Figure S12). When compared with sucralfate, combination 5-ASA/steroid did not improve the endoscopic Gilinsky score (one trial; 22 participants; risk ratio 0.66, 95% confidence interval 0.35 to 1.23) [39] (see Supplementary Figure S13). Compared with no metronidazole, the number of people with improved bleeding after 4 weeks of treatment was improved by metronidazole (one trial; 60 participants; risk ratio 1.5, 95% confidence interval 1.09 to 2.06) [13] (see Supplementary Figure S14). Compared with placebo, pentoxifylline did not improve grade 2 Common Terminology Criteria for Adverse Events (CTCAE) bleeding score (one trial; eight participants; risk ratio 0.90, 95% confidence interval 0.31 to 2.63) [32] (see Supplementary Figure S15). Compared with standard care, pentoxifylline did not lead to cessation of bleeding after 1 week (one trial; 40 participants; risk ratio 1.33, 95% confidence interval 0.88 to 2.03) [47] (see Supplementary Figure S16). When SCFA was compared with placebo, there was no difference in the mean number of days of per rectal bleeding per week (one trial; 16 participants; mean difference −2.00, 95% confidence interval −4.4 to 0.4) [54] (see Supplementary Figure S17).

Other Clinical Outcomes

When compared with no probiotics, probiotics did not improve abdominal pain (one trial; 34 participants; risk ratio 0.89, 95% confidence interval 0.58 to 1.37) [50] (see Supplementary Figure S18). When compared with placebo, pentoxifylline/vitamin E did not improve faecal incontinence (one trial; 31 participants; risk ratio 1.03, 95% confidence interval 0.56 to 1.89) [32] (see Supplementary Figure S19). When compared with APC, sucralfate did not improve self-reported tenesmus (one trial; 130 participants; risk ratio 1.41, 95% confidence interval 0.56 to 3.52) [45] (see Supplementary Figure S20).

Quality of Life

Formalin did not improve quality of life compared with APC (one trial; 27 participants; mean difference 0.31, 95% confidence interval −0.13 to 0.75) [34] (see Supplementary Figure S21). HBOT did not improve quality of life compared with placebo (one trial; 119 participants; mean difference 0.18, 95% confidence interval −7.78 to 8.14) [53] (see Supplementary Figure S22). Two trials dichotomised quality of life data (improvement versus no improvement). Sucralfate improved quality of life compared with 5-ASA/steroids (one trial; 32 participants; risk ratio 0.57, 95% confidence interval 0.35 to 0.92) [39]. The addition of dietary counselling to usual care did not increase quality of life (one trial; 150 participants; risk ratio 1.67, 95% confidence interval 0.88 to 3.16) [51]. One trial did not report usable quality of life data [31] and one trial reported no difference in quality of life scores between treatment (vitamin E) and placebo groups, but no data were provided [32].

Adverse Events

Six studies did not report adverse events [31,36,46,49,51,52]. Six further studies explicitly reported observing no complications [12–14,44,45,48]. Formalin studies observed anorectal pain in 33% participants [40], temporary anorectal discomfort in 87% [41] and worsening incontinence in 21% [55]. The higher concentrations of formalin were associated with increased pain, vaginal fistula and deep ulcerations [37]. HBOT was most commonly associated with mostly transient eye refractive changes (3.3%), ear pain (15.8%) and confinement anxiety (1.7%) [38,53]. One study reported that APC-related ulcers were present in as many as 60% of patients, with 10% symptomatic [43]. Other events

associated with APC included stenosis, mild anal pain and worsening of bleeding [34,35,43].

Summary of Findings

The certainty of the evidence for gastrointestinal symptom score outcomes within eight comparisons were typically graded as moderate or low (Table 2). For APC versus sucralfate, formalin versus sucralfate, formalin versus antibiotics, 4% versus 10% formalin, APC versus APC with medication, probiotics/antibiotics versus placebo and pentoxifylline/vitamin E versus placebo, the certainty of evidence for gastrointestinal symptom scores was graded as moderate due to within-study risks of bias. APC versus formalin was graded as having a very low certainty of evidence for gastrointestinal symptom scores. Finally, nearly all trials included a small number of participants.

Discussion

This review identified 28 studies (2392 participants), of varying methodological quality, that have assessed non-surgical interventions for the management of late gastrointestinal symptoms following pelvic radiotherapy. One surgical trial was identified, which was ongoing at the time of this review and, therefore, was not included in the analysis [29]. It adds 12 studies to the last Cochrane review on this subject (2016), although our eligibility criteria were not restricted to rectal disease [11]. Findings from our work do support certain interventions (including APC, formalin, counselling and metronidazole) having promise. However, interpretation of benefit needs to be considered with caution, with studies frequently being single centre and excluding important outcomes measures, such as quality of life. The use of formalin (4%) had the greatest efficacy with regards to improving

Table 2
Certainty of evidence for gastrointestinal symptom scores

Intervention type	No. participants (studies)	Certainty of the evidence (grade)	Relative effect (95% confidence interval)
APC versus formalin	57 (2 RCTs)	⨁◯◯◯ Very low*	SMD **0.00 SD** (0.52 lower to 0.52 higher)
APC versus sucralfate	130 (1 RCT)	⨁⨁⨁◯ Moderate†	SMD **1.22 SD higher** (0.84 higher to 1.59 higher)
APC versus RFA	7 (1 RCT)	⨁◯◯◯ Very low‡	Not estimable
Formalin versus sucralfate	102 (1 RCT)	⨁⨁⨁◯ Moderate§	SMD **1.07 SD lower** (1.48 lower to 0.65 lower)
Formalin versus antibiotics	34 (1 RCT)	⨁⨁⨁◯ Moderate¶	SMD **0.27 SD lower** (0.95 lower to 0.40 higher)
4% formalin versus 10% formalin	115 (1 RCT)	⨁⨁⨁◯ Moderate‖	SMD **0.28 SD higher** (0.08 lower to 0.65 higher)
APC versus APC with medication	122 (1 RCT)	⨁⨁⨁◯ Moderate**	SMD **0.00 SD** (0.35 lower to 0.35 higher)
Vitamin A versus placebo	17 (1 RCT)	⨁⨁⨁◯ Moderate††	SMD **1.43 SD lower** (2.53 lower to 0.33 lower)
Pentoxifylline/vitamin E versus placebo	51 (1 RCT)	⨁⨁⨁◯ Moderate‡‡	SMD **0.17 SD lower** (0.73 lower to 0.4 higher)
Hyperbaric oxygen therapy versus control	204 (2 RCTs)	⨁◯◯◯ Very low§§	SMD **0.21 SD lower** (0.95 lower to 0.52 higher)

APC, argon plasma coagulation; RCT, randomised controlled trial; RFA, radiofrequency ablation; SD, standard deviation; SMD, standardised mean difference.

* Downgraded two levels due to study limitations: high risk of bias; issues with randomisation in one trial and unclear risk of bias in blinding, attrition and selective reporting, high risk of bias for performance and detection bias in the other trial and unclear risk of bias in selective reporting. Downgraded one level due to imprecision: 95% confidence interval included null effect.

† Downgraded one level due to study limitations: unclear risk of bias.

‡ Downgraded two levels due to study limitations: unclear risk of bias and imprecision; relative effect not estimable due to small number of participants (7).

§ Downgraded one level due to study limitations: inadequate patient and personnel blinding leading to high risk of performance bias and unclear reporting bias.

¶ Downgraded one level due to imprecision: small number of participants and 95% confidence interval included null effect.

‖ Downgraded one level due to imprecision: 95% confidence interval included null effect.

** Downgraded one level due to imprecision: 95% confidence interval included null effect.

†† Downgraded one level due to imprecision: small number of participants (17).

‡‡ Downgraded one level due to imprecision: 95% confidence interval included null effect.

§§ Downgraded one level due to study limitations: unclear risk of bias. Downgraded one level due to imprecision: 95% confidence interval included null effect. Downgraded one level due to inconsistency: $I^2 = 84\%$.

symptoms in this review, with APC alone (as compared with APC and sucralfate) offering the greatest benefit for the management of rectal bleeding. However, it is to be recognised that although efficacy was greatest for APC, it was associated with adverse events, which included anorectal pain in 33%, temporary anorectal discomfort in 87% and worsening incontinence in 21%.

Although our systematic review provides a contemporary oversight of all endoscopic, comparative medical and systemic therapies used in managing late gastrointestinal symptoms over the past 30 years, it is limited by a paucity of well-conducted randomised controlled studies. Poor reporting, clinical and methodological heterogeneity made statistical synthesis difficult, with sample sizes, treatment duration and outcome measures varying between each study assessed, and some studies dichotomising continuous outcomes [39,51]. Furthermore, broad outcome measures, such as overall symptom score, challenge study comparisons, with study interventions likely to have targeted specific pathology or symptoms. Another limitation to our work is that the review was limited to English-language studies only, which may have introduced a language bias. Most studies in the review also had high or an unclear risk of bias in at least one domain. Four of these had high risk in outcome data and selective reporting, which could have influenced the analysis [13,30,32,38]. Attempts were made to contact the relevant authors to acquire raw data, but these attempts were unsuccessful, leading to a potential non-reporting bias. As publication and reporting biases typically favour positive results, this is unlikely to affect any comparisons that showed little or no difference between treatments.

Conclusions

There are numerous, unproven or ineffective treatment options being used in clinical practice for the treatment of gastrointestinal toxicity following pelvic radiotherapy. Shared decision-making should focus on giving patients a clear understanding of the risks and benefits of interventions being used, and available alternatives. This careful counselling should consider patient preferences, related comorbidities, life expectancy and local availability of treatment options, which can preferentially determine treatment modality. The Andreyev study suggests that an algorithm-based treatment can improve the quality of decision-making [31] and further research is warranted in this regard.

The effects of pelvic radiation are heterogeneous in their presentation and definition, with radiation proctitis, radiation colitis, radiation proctopathy and, recently, pelvic radiation disease, all used to define the cluster of symptoms, including per rectal bleeding, pelvic pain, incontinence, tenesmus and diarrhoea [56]. Standardisation of terminology and grading is needed to make the results of studies comparable. Of 29 studies, three used Radiation Therapy Oncology Group European Organization for Research and Treatment of Cancer (RTOG EORTC) [31,32,34], five used Late Effects of Normal Tissues-Subjective, Objective, Management, Analytic (LENT-SOMA) [30,31,38,48,53] and two used the CTCAE grading system [32,38] (some trials used more than one scoring system). A core outcome set is desirable to standardise future research [57,58].

Further research should also concentrate on quality of life, tolerability of interventions and preference for various treatments. A paper by Ludlow [59] showed that patients who suffered from pelvic radiation disease experienced feelings of stigma, poor awareness from healthcare professionals and lacked support from family and friends. Hence, support from specialist professionals and specialised clinic, support groups and family, should be used to influence patient choice of treatment. In addition, there are also no resource utilisation or cost-effectiveness studies evaluating assessed interventions.

We propose that patients with late gastrointestinal symptoms following radiotherapy be managed in regional centres with an interest in radiation-associated disease and gastrointestinal toxicity. This would help facilitate the conduct of larger intervention studies, which could better inform the efficacy and economics of differing interventions. The merits of this approach would help to ensure an evidence-based approach to the management of this condition, which is increasing in prevalence, and is currently being managed in diverse ways. Further research should also explore the fundamental pathology, followed by refined categorisation. This should precede meticulously planned clinical trials addressing each symptom/pathology in a systematic and rational manner, which could help the development of a core outcome set.

Data Availability

Data supporting the results reported in the article, including forest plots, can be found in the supporting information.

Author Contributions

MK conceived the review. The review was designed by HB, DH and MK. AT, LS, MM ran searches and screened studies supported by DH, MB and HB. AT, LS, MM, WST and HB extracted data, supported by DH, MB and MK. AT and DH undertook the analysis, supported by MB. WST, HB, MK and DH compiled the GRADEpro summary of findings tables. HB, DH, AT and MK prepared the manuscript and all authors read, commented on and approved the final draft.

Conflicts of Interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2024.02.011.

References

[1] Grodsky M, Sidani S. Radiation proctopathy. *Clin Colon Rectal Surg* 2015;28:103–111. https://doi.org/10.1055/s-0035-1547337.

[2] Ahmed M, Ahmed R. Radiation in gastroenterology. *Gastroenterol Res* 2022;15:285–296. https://doi.org/10.14740/gr1567.

[3] Hauer-Jensen M, Wang J, Boerma M, Fu Q, Denham JW. Radiation damage to the gastrointestinal tract: mechanisms, diagnosis, and management. *Curr Opin Support Palliat Care* 2007;1:23–29. https://doi.org/10.1097/SPC.0b013e3281108014.

[4] Dahiya DS, Kichloo A, Tuma F, Albosta M, Wani F. Radiation proctitis and management strategies. *Clin Endosc* 2022;55:22–32. https://doi.org/10.5946/ce.2020.288.

[5] Andreyev HJN. Gastrointestinal problems after pelvic radiotherapy: the past, the present and the future. *Clin Oncol* 2007;19:790–799. https://doi.org/10.1016/j.clon.2007.08.011.

[6] Sher DJ. Cost-effectiveness studies in radiation therapy. *Expert Rev Pharmacoecon Outcome. Res* 2010;10:567–582. https://doi.org/10.1586/erp.10.51.

[7] Shadad AK. Gastrointestinal radiation injury: symptoms, risk factors and mechanisms. *World J Gastroenterol* 2013;19:185. https://doi.org/10.3748/wjg.v19.i2.185.

[8] Paquette IM, Vogel JD, Abbas MA, Feingold DL, Steele SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the treatment of chronic radiation proctitis. *Dis Colon Rectum* 2018;61:1135–1140. https://doi.org/10.1097/DCR.0000000000001209.

[9] Lee JK, Agrawal D, Thosani N, Al-Haddad M, Buxbaum JL, Calderwood AH, *et al.* ASGE guideline on the role of endoscopy for bleeding from chronic radiation proctopathy. *Gastrointest Endosc* 2019;90:171–182.e1. https://doi.org/10.1016/j.gie.2019.04.234.

[10] Andreyev HJN, Muls AC, Norton C, Ralph C, Watson L, Shaw C, *et al.* Guidance: The practical management of the gastrointestinal symptoms of pelvic radiation disease. *Frontline Gastroenterol* 2015;6:53–72. https://doi.org/10.1136/flgastro-2014-100468.

[11] van de Wetering FT, Verleye L, Andreyev HJN, 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 Syst Rev* 2016;2016. https://doi.org/10.1002/14651858.CD003455.pub2.

[12] Jensen DM, Machicado GA, Cheng S, Jensen ME, Jutabha R. A randomized prospective study of endoscopic bipolar electrocoagulation and heater probe treatment of chronic rectal bleeding from radiation telangiectasia. *Gastrointest Endosc* 1997;45:20–25. https://doi.org/10.1016/S0016-5107(97)70298-0.

[13] Cavcić J, Turcić J, Martinac P, Jelincić Z, Zupancić B, Panijan-Pezerović R, *et al.* Metronidazole in the treatment of chronic radiation proctitis: clinical trial. *Croat Med J* 2000;41:314–318.

[14] Ehrenpreis ED, Jani A, Levitsky J, Ahn J, Hong J. A prospective, randomized, double-blind, placebo-controlled trial of retinol palmitate (vitamin A) for symptomatic chronic radiation proctopathy. *Dis Colon Rectum* 2005;48:1–8. https://doi.org/10.1007/s10350-004-0821-7.

[15] Higgins JPT, Savović J, Page MJ, Sterne JAC, RoB2 Development Group. *Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)* 2019.

[16] Drahota A, Beller E. RevMan calculator n.d.

[17] McGrath S, Zhao X, Steele R, Thombs BD, Benedetti A. The DEPRESsion Screening Data (DEPRESSD) Collaboration et al. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. *Stat Methods Med Res* 2020;29:2520–2537. https://doi.org/10.1177/0962280219889080.

[18] Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13. https://doi.org/10.1186/1471-2288-5-13.

[19] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135. https://doi.org/10.1186/1471-2288-14-135.

[20] *Review Manager (RevMan)* 2020.

[21] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trial.* 1986;7:177–188. https://doi.org/10.1016/0197-2456(86)90046-2.

[22] Schünemann HJ, Higgins JPT, Vist GE, Glasziou P, Akl EA, Skoetz N, Guyatt GH. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Available from: www.training.cochrane.org/handbook.

[23] GRADEpro n.d.

[24] Triantafillidis JK, Dadioti P, Nicolakis D, Mericas E. High doses of 5-aminosalicylic acid enemas in chronic radiation proctitis: comparison with betamethasone enemas. *Am J Gastroenterol* 1990;85:1537–1538.

[25] Hendrix P, Cahow E. Chronic radiation enteritis. *Gastroenterologist* 1994;2:70–73.

[26] Rougier PH, Zimmerman P, Pignon JP, Kac J, Crespon B, Zrihen E, *et al.* Rectites radiques: efficacité comparée de deux types de corticoïdes administrés localement. *Méd Chir Dig* 1992;21:91–93.

[27] Andreyev HJN. ISRCTN22890916: the effective management of radiation-induced bowel injury: a randomised controlled trial n.d.

[28] Andreyev HJN. ISRCTN33398289: a 2 x 2 randomised, double blind, placebo controlled trial of pentoxifylline (trental) +/- high dose vitamins for radiation induced bowel toxicity: the ROBOTS 2 trial n.d.

[29] *Ma T PE-Bacon for late complications of chronic radiation-induced rectal injury (PE-Bacon)* 2022.

[30] Sidik S, Hardjodisastro D, Setiabudy R, Gondowiardjo S. Does hyperbaric oxygen administration decrease side effect and improve quality of life after pelvic radiation? *Acta Med Indones* 2007;39:169–173.

[31] Andreyev HJN, Benton BE, Lalji A, Norton C, Mohammed K, Gage H, *et al.* Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial. *Lancet* 2013;382:2084–2092. https://doi.org/10.1016/S0140-6736(13)61648-7.

[32] Andreyev HJN, Matthews J, Adams C, Gothard L, Lucy C, Tovey H, *et al.* Randomised single centre double-blind placebo controlled phase II trial of Tocovid SupraBio in combination with pentoxifylline in patients suffering long-term gastrointestinal adverse effects of radiotherapy for pelvic cancer: the PPALM study. *Radiother Oncol* 2022;168:130–137. https://doi.org/10.1016/j.radonc.2022.01.024.

[33] Talley NA, Chen F, King D, Jones M, Talley NJ. Short-chain fatty acids in the treatment of radiation proctitis: a randomized,

double-blind, placebo-controlled, cross-over pilot trial. *Dis Colon Rectum* 1997;40:1046–1050. https://doi.org/10.1007/BF02050927.

[34] Furtado FS, Furtado GB, Oliveira AT, Oliveira FAA, Pinho CS, Sampaio JPA, *et al*. Endorectal formalin instillation or argon plasma coagulation for hemorrhagic radiation proctopathy therapy: a prospective and randomized clinical trial. *Gastrointest Endosc* 2021;93:1393–1400. https://doi.org/10.1016/j.gie.2020.11.007.

[35] Lenz L, Tafarel J, Correia L, Bonilha D, Santos M, Rodrigues R, *et al*. Comparative study of bipolar electrocoagulation versus argon plasma coagulation for rectal bleeding due to chronic radiation coloproctopathy. *Endoscopy* 2011;43:697–701. https://doi.org/10.1055/s-0030-1256467.

[36] Germain I, Desjardins J, Demers M, Dagnault A. Phase III study: impact of probiotics on diarrhea in patients treated with pelvic radiation. *Int J Radiat Oncol Biol Phys* 2011;81:S667–S668. https://doi.org/10.1016/j.ijrobp.2011.06.916.

[37] Guo G-H, Yu F-Y, Wang X-J, Lu F. A randomized controlled clinical trial of formalin for treatment of chronic hemorrhagic radiation proctopathy in cervical carcinoma patients. *Support Care Cancer* 2015;23:441–446. https://doi.org/10.1007/s00520-014-2401-2.

[38] Glover M, Smerdon GR, Andreyev HJ, Benton BE, Bothma P, Firth O, *et al*. Hyperbaric oxygen for patients with chronic bowel dysfunction after pelvic radiotherapy (HOT2): a randomised, double-blind, sham-controlled phase 3 trial. *Lancet Oncol* 2016;17:224–233. https://doi.org/10.1016/S1470-2045(15)00461-1.

[39] Kochhar R, Patel F, Sharma SC, Ayyagari S, Aggarwal R, Goenka MK, *et al*. Radiation-induced proctosigmoiditis: prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate. *Dig Dis Sci* 1991;36:103–107. https://doi.org/10.1007/BF01300096.

[40] Nelamangala Ramakrishnaiah VP, Javali TD, Dharanipragada K, Reddy KS, Krishnamachari S. Formalin dab, the effective way of treating haemorrhagic radiation proctitis: a randomized trial from a tertiary care hospital in South India: formalin dab in radiation proctitis. *Colorectal Dis* 2012;14:876–882. https://doi.org/10.1111/j.1463-1318.2012.03008.x.

[41] Sahakitrungruang C, Patiwongpaisarn A, Kanjanasilp P, Malakorn S, Atittharnsakul P. A randomized controlled trial comparing colonic irrigation and oral antibiotics administration versus 4% formalin application for treatment of hemorrhagic radiation proctitis. *Dis Colon Rectum* 2012;55:1053–1058. https://doi.org/10.1097/DCR.0b013e318265720a.

[42] Pui WC, Chieng TH, Siow SL, Nik Abdullah NA, Sagap I. A randomized controlled trial of novel treatment for hemorrhagic radiation proctitis. *Asian Pac J Cancer Prev* 2020;21:2927–2934. https://doi.org/10.31557/APJCP.2020.21.10.2927.

[43] Chruscielewska-Kiliszek MR, Regula J, Polkowski M, Rupinski M, Kraszewska E, Pachlewski J, *et al*. Sucralfate or placebo following argon plasma coagulation for chronic radiation proctitis: a randomized double blind trial: treatment of chronic radiation proctitis. *Colorectal Dis* 2013;15:e48–e55. https://doi.org/10.1111/codi.12035.

[44] Merino Rodríguez B, Gonzalez Asanza C, Nogales Rincón O, Klimova K, Ibáñez L, Díaz Fontenla F, *et al*. Does the topical treatment can shorten the duration of treatment with APC in radiation proctitis. *United Eur Gastroenterol J* 2013;1:A175.

[45] Sirikurnpiboon S, Wannaprasert J, Ratanachu-ek T. Randomized control trial comparing management of radiation proctocolitis with sucralfate instillation via colonoscopy and argon plasma coagulation. *J Med Assoc Thai* 2019;102:104.

[46] Oliner C, Pinkhasov M, Lawlor G. Efficacy of radiofrequency coagulation in managing chronic radiation proctitis. *Am J Gastroenterol* 2012;107:S735–S736.

[47] Venkitaraman R, Coffey J, Norman AR, James FV, Huddart RA, Horwich A, *et al*. Pentoxifylline to treat radiation proctitis: a small and inconclusive randomised trial. *Clin Oncol* 2008;20:288–292. https://doi.org/10.1016/j.clon.2008.01.012.

[48] Yeoh E, Tam W, Schoeman M, Moore J, Thomas M, Botten R, *et al*. Argon plasma coagulation therapy versus topical formalin for intractable rectal bleeding and anorectal dysfunction after radiation therapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys* 2013;87:954–959. https://doi.org/10.1016/j.ijrobp.2013.08.034.

[49] Kayal A, Weiss A. A284 Argon plasma coagulation alone or in combination with hemospray for radiation proctitis. *J Can Assoc Gastroenterol* 2018;1:492. https://doi.org/10.1093/jcag/gwy008.285.

[50] Henriksson R, Franzén L, Sandström K, Nordin A, Arevärn M, Grahn E. Effects of active addition of bacterial cultures in fermented milk to patients with chronic bowel discomfort following irradiation. *Support Care Cancer* 1995;3:81–83. https://doi.org/10.1007/BF00343926.

[51] Forslund M, Ottenblad A, Ginman C, Johansson S, Nygren P, Johansson B. Effects of a nutrition intervention on acute and late bowel symptoms and health-related quality of life up to 24 months post radiotherapy in patients with prostate cancer: a multicentre randomised controlled trial. *Support Care Cancer* 2020;28:3331–3342. https://doi.org/10.1007/s00520-019-05182-5.

[52] Kronberger IEK. A multicenter, randomized, double blind placebo controlled trial of micronized purified flavonoid-fraction (MPFF) in the management of radiation proctitis [internet]. clinicaltrials.gov; 2020 Oct [cited 2024 Feb 20]. Report No.: NCT04335617. Available from: https://classic.clinicaltrials.gov/ct2/show/results/NCT04335617.

[53] Clarke RE, Tenorio LMC, Hussey JR, Toklu AS, Cone DL, Hinojosa JG, *et al*. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008;72:134–143.e15. https://doi.org/10.1016/j.ijrobp.2007.12.048.

[54] Pinto A, Fidalgo P, Cravo M, Midões J, Chaves P, Rosa J, *et al*. Short chain fatty acids are effective in short-term treatment of chronic radiation proctitis: randomized, double-blind, controlled trial. *Dis Colon Rectum* 1999;42:788–795. https://doi.org/10.1007/BF02236937.

[55] Singhal M, Kapoor A, Narayan S, Nirban RK, Maharia S, Harsh KK, *et al*. Comparison of benefits, safety of 8% versus 4% formalin for treatment of chronic hemorrhagic radiation proctitis in patients of cervical carcinoma: a randomized controlled trial. *Support Care Cancer* 2015;23:S338. https://doi.org/10.1007/s00520-015-2712-y.

[56] Andreyev HJN, Wotherspoon A, Denham JW, Hauer-Jensen M. Pelvic radiation disease: new understanding and new solutions for a new disease in the era of cancer survivorship. *Scand J Gastroenterol* 2011;46:389–397. https://doi.org/10.3109/00365521.2010.545832.

[57] Clarke M, Williamson P. Core outcome sets and trial registries. *Trials* 2015;16:216. https://doi.org/10.1186/s13063-015-0738-6.

[58] Prinsen CAC, Vohra S, Rose MR, Boers M, Tugwell P, Clarke M, *et al*. How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" – a practical guideline. *Trials* 2016;17:449. https://doi.org/10.1186/s13063-016-1555-2.

[59] Ludlow H. Gastrointestinal symptoms of pelvic radiation disease (part 2): impact on patients and carers. *Gastrointest Nurs* 2020;18:44–49. https://doi.org/10.12968/gasn.2020.18.3.44.