Interventions for managing late gastrointestinal symptoms following pelvic radiotherapy: A systematic review of randomised and non-randomised trials

(Version 1.0, 09.07.2021)

Contact

Dr Matthew Kurien
m.kurien@sheffield.ac.uk
University of Sheffield

Prof Daniel Hind
d.hind@sheffield.ac.uk
University of Sheffield

Contributions of Protocol Authors

Matthew Kurien and Daniel Hind conceived the review. MK and DH and Hannah Berntsson designed the review. Amy Thien, Mahia Mahzabin, Laura Stewart and HB will be primarily responsible for the acquisition of the data. MK, DH, AT and HB will analyse and interpret the data.

MK and DH drafted the review protocol and revised it critically for important intellectual content. MK and DH will draft review reports and revise them critically for important intellectual content.

MB and DH gave final approval of the version to be published.

MB, DH, AT, and HB agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Guarantor of the review

Matthew Kurien

Introduction

22,000 people have pelvic radiotherapy for urological, gastrointestinal and gynaecological malignancies each year in the UK.[1] This is delivered as a primary treatment, combined with chemotherapy, or used before or after surgery. Although radiotherapy is targeted at the malignancy, invariably adjacent organs and normal tissue are exposed to radiation during treatment. The small and large bowel are commonly exposed as they occupy a large amount of the abdominal and pelvic cavity. This radiation can lead to bowel injury, with the degree of injury being influenced by both radiotherapy (e.g. dosing, type of radiation, size and site of the treatment field) and non-radiotherapy factors (e.g. concomitant illnesses, other treatments, genetics).[2]

Radiation-induced gastrointestinal tissue injury commonly leads to the development of gastrointestinal symptoms, which may be acute (occurring during radiotherapy or within three months) or chronic (persisting or appearing after three months). The acute symptoms can include diarrhoea, abdominal pain, nausea, bloating and rectal bleeding. These symptoms often improve following cessation of radiotherapy, however their presence may influence both the scheduling and dosing of radiotherapy, with an increased likelihood of developing late gastrointestinal effects.[3] The late (chronic) gastrointestinal symptoms are widely recognised, and include bowel urgency, rectal bleeding, flatulence, abdominal pain and faecal incontinence. These symptoms have been reported to influence quality of life, and may be a manifestation of other gastrointestinal disorders, such as bile acid diarrhoea and small bowel bacterial overgrowth, which become more prevalent following radiotherapy treatment.[4]

Treatment approaches to manage these chronic gastrointestinal symptoms and their efficacy currently remains uncertain. Previous work evaluating outcomes has tended to focus on specific late effects (e.g. radiation proctitis (proctopathy)) or been restricted to specific pelvic cancers.[5 6] Currently, UK practice is informed by a practical guideline, which was developed by experts that manage patients with pelvic radiation disease.[7] Although these guidelines have tried to standardise care, there exists a significant knowledge gap regarding the efficacy of some the treatments currently advocated.

Aim

The aim of this review is to identify and examine the effectiveness of interventions used for managing gastrointestinal symptoms in adults who have received pelvic radiotherapy.

Specific Objectives

A systematic review examining the clinical effectiveness of treatments for the management of late effects of pelvic radiotherapy.

Methods

Eligibility Criteria

Our criteria for considering studies for this review are detailed in the following sections.

Types of studies

Randomised controlled trials (RCTs).

Types of Participants

Patients must have been diagnosed with a pelvic malignancy and undergone pelvic radiotherapy. They must have gastrointestinal symptoms continuing from completion of radiotherapy for more than three months, or occurring more than three months after the completion of radiotherapy. Symptoms which constitute population eligibility are one or more of the following:

- Rectal bleeding
- Diarrhoea
- Faecal incontinence

Types of Interventions

Interventions used to treat gastrointestinal symptoms following pelvic radiotherapy, including

- Pharmacological interventions (e.g. sucralfate enemas, 5-aminosalicylates, antibiotics);
- Non-pharmacological interventions, including dietary modifications (e.g. macronutrients, dietary fibre, probiotics, biofeedback);
- Endoscopic interventions (e.g. Argon Plasma Coagulation)

Comparators for the interventions described are placebos, no active intervention (standard of care), or alternative interventions.

Report Characteristics

This review will focus on studies published in the English language between January, 1990, and September, 2021.

Information Sources

We will search MEDLINE, EMBASE, CINAHL, Cochrane Library from 1990 to February 2022. We will search trial registers. We will not contact study authors.

Search Strategy

1. Radiation Injuries/
2. Radiation.mp.
3. Radiotherapy.mp.

4. 1 or 2 or 3
5. Gastrointestinal Hemorrhage/
6. Proctitis/
7. Inflammatory bowel diseases/
8. Chronic Disease.mp.
9. Proctocolitis/
10. Telangiectasis/
11. 5 or 6 or 7 or 8 or 9 or 10
12. Argon Plasma Coagulation.mp.
13. Argon Plasma Coagulation/
14. Formaldehyde/
15. Endorectal formalin instillation.mp.
16. EFI.mp.
17. Nutrition.mp.
18. Metronidazole/
19. Mesalamine/
20. Anti-Infective Agents/
21. Anti-Inflammatory Agents/
22. Anti-Inflammatory Agents, Non-Steroidal/
23. Betamethasone/
24. Butyrates/
25. Butyric Acid/
26. Fatty Acids, Volatile/
27. Fatty Acids.mp.
28. Drug Therapy, Combination.mp
29. Prednisolone/
30. Sucralfate/
31. Sulfasalazine/
32. Electrocoagulation/
33. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. 4 and 11 and 33

The search will be limited to papers published in the English language, between January, 1990, and February 2022.

We will also check the reference lists of eligible citations for further studies.

Data collection and management

Data abstraction processes will be piloted before the review. Citations will be downloaded into Rayyan or Mendeley reference management software to aid recording of eligibility assessment. Data from eligible studies will then be extracted directly into Google Sheets by two reviewers and checked by two further reviewers.

Selection Process

Two reviewers will screen the title and abstracts of the studies collected according to the eligibility criteria.

Two reviewers will review the full text of the studies that were deemed eligible at the abstract and title stage and select those eligible for inclusion in the analysis according to the eligibility criteria, checking eligibility with two other reviewers.

Two reviewers will independently extract data from the studies eligible for analysis.

We will present a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart of our study selection process.[20,21]

Data items

Information will be extracted from eligible studies on:
(1) characteristics of study participants, (including age, type of cancer, type and dosing of radiotherapy) and the study's eligibility criteria.
(2) intervention characteristics (type, dose, duration) and character of comparator.
(3) outcome measures (including symptoms scores, quality of life scores (using validated scales), length of follow up, unintended effects of treatment, number of people requiring more invasive treatment).

Outcomes and prioritisation

Studies should include one of the following outcome measures:

Primary outcome

1. Overall Gastrointestinal symptom score according to the Gastrointestinal Symptom Rating Scale (GSRS), Inflammatory Bowel Disease Questionnaire-bowel function dimension (IBDQ-BD), or another scale.

2. Moderate or severe GI symptoms (toxicity) according to the Common Terminology Criteria for Adverse Events, European Organisation for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) scoring system, GSRS or another scale, including:
    - Diarrhoea (the passage of frequent, loose stools);
    - Faecal incontinence (stool leakage);
    - Faecal urgency (a sudden need to pass stool);
    - Rectal bleeding;
    - Tenesmus (a sensation of incomplete evacuation);
    - Abdominal pain/cramps;
    - Flatulence;

- Weight loss.

3. Quality of life (QoL) score, according to EORTC QLQ-C30, QLQ-PR25, Prostate Cancer Quality of Life Scale (PC-QOL), EQ-5D or another scale.

Secondary outcomes

1. Patient Acceptability
2. Patient Satisfaction
3. Medication use for symptom management

Risk of bias in individual studies

We will separately assess the potential for systematic error within individual studies using the Cochrane risk of bias tool and the following dimensions of methodological quality: (1) generation of allocation sequence; (2) allocation concealment; (3) blinding (participant and researchers); (4) blinding of outcome assessors; (5) completeness of outcome data. Studies will be graded as being at, “low”, “high” or “unclear” risk of bias. Any discrepancies will be discussed amongst team members until a unanimous decision is reached.

Synthesis

Where more than one study evaluates comparable interventions and reports the same outcome meta-analyses will be undertaken. All meta-analyses will be carried out in RevMan 5 using a random effects model. As studies are likely to assess self-reported gastrointestinal symptoms and quality of life using different scales we will pool estimates of clinical effect using the standardised mean difference (SMD) in which the size of the intervention effect is represented in units of the standard deviations (SD). Conventionally, values of 0.20, 0.50, and 0.80 indicate, respectively, small, medium, and large effects. Where non-reported outcome data cannot be imputed, the effect sizes will be deemed not estimable. Where adverse effects are reported as dichotomous data, we will pool data using a DerSimonian and Laird inverse variance method.

We will use I^2 to measure the amount of between-study variation in effect estimates which cannot be explained by the play of chance alone (statistical heterogeneity). By convention, I^2 values of 25%, 50%, and 75% denote low, moderate, and high levels of inconsistency.

Meta-bias(es)

If enough studies (≥10) evaluate the same intervention and report the same outcome funnel plots will be produced to identify small study effects and assess the risk of publication bias.

Confidence in cumulative evidence

The quality of the evidence for each prespecified outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

References

1. Facts about Pelvic Radiation Disease in the UK, Pelvic Radiation Disease Association. February 2021 http://www.prda.org.uk/information-health-professionals/.
2. Andreyev J. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. *Lancet Oncol* 2007;8(11):1007-17. doi: 10.1016/S1470-2045(07)70341-8 [published Online First: 2007/11/03]
3. Barnett GC, De Meerleer G, Gulliford SL, et al. The impact of clinical factors on the development of late radiation toxicity: results from the Medical Research Council RT01 trial (ISRCTN47772397). *Clin Oncol (R Coll Radiol)* 2011;23(9):613-24. doi: 10.1016/j.clon.2011.03.001 [published Online First: 2011/04/08]
4. Kurien M, Thurgar E, Davies A, et al. Challenging current views on bile acid diarrhoea and malabsorption. *Frontline Gastroenterol* 2018;9(2):92-97. doi: 10.1136/flgastro-2017-100808 [published Online First: 2018/03/29]
5. Denton AS, Andreyev HJ, Forbes A, et al. Systematic review for non-surgical interventions for the management of late radiation proctitis. *Br J Cancer* 2002;87(2):134-43. doi: 10.1038/sj.bjc.6600360 [published Online First: 2002/07/11]
6. Sipaviciute A, Sileika E, Burneckis A, et al. Late gastrointestinal toxicity after radiotherapy for rectal cancer: a systematic review. *Int J Colorectal Dis* 2020;35(6):977-83. doi: 10.1007/s00384-020-03595-x [published Online First: 2020/04/17]
7. Andreyev HJ, Muls AC, Norton C, et al. Guidance: The practical management of the gastrointestinal symptoms of pelvic radiation disease. *Frontline Gastroenterol* 2015;6(1):53-72. doi: 10.1136/flgastro-2014-100468 [published Online First: 2015/01/13]