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2023

REVIEW ARTICLE

Royal Australasian College of Surgeons

Long-term adverse effects and healthcare burden of rectal cancer radiotherapy: systematic review and meta-analysis

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Key words
complications, obstruction, radiotherapy, rectal cancer.

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Accepted for publication 8 September 2022.

doi: 10.1111/ans.18059

Abstract

Background: As rectal cancer survival increases, more patients survive with potentially severe, long-term gastrointestinal and genitourinary complications from radiotherapy. The burden of these complications for patients and healthcare services is unclear, which this review aims to quantify.
Methods: Systematic search of Medline and Embase for randomized-controlled trials (RCTs) and multicentre observational studies published since 2000, reporting hospitalization/procedural intervention for long-term (>6 months post-treatment) gastrointestinal or genitourinary complications after radiotherapy and surgery for rectal cancer. Prevalence values were pooled in a meta-analysis assuming random effects. Organ-preservation patients were excluded.
Results: 4044 records screened; 24 reports from 23 studies included (15 RCTs, 8 Observational), encompassing 15 438 patients. Twenty-one studies (median follow-up 60 months) reported gastrointestinal complications post-radiotherapy: pooled prevalence 11% (95% confidence interval (95% CI) 8–14%). Thirteen reported small bowel obstruction: prevalence 9% (95% CI 6–12%), a 58% increased risk compared with surgery alone (RR 1.58, 95% CI 1.26–1.98, $n = 5$ studies). Seven reported fistulas: prevalence 1% (95% CI 1–2%). Thirteen reported genitourinary complications: prevalence 4% (95% CI 1–6%); RR 1.10 (95% CI 0.88–1.38, $n = 3$ studies) compared with surgery alone.
Conclusions: Over 10% of patients are hospitalized for long-term complications following rectal cancer radiotherapy. Serious gastrointestinal complications are commonplace; late small bowel obstruction is more common in patients having radiotherapy and surgery compared with surgery alone. Patients and clinicians need to be aware of these risks.

Introduction

Rectal cancer is the eighth most common cancer globally, with ~700 000 cases a year and 310 000 deaths.[1] Survival has been increasing, in part due to total mesorectal excision and evolving use of radiotherapy.[2,3] In England, ~40% of patients with rectal cancer receive radiotherapy.[4] Treatment started to standardize in the early-2000s, as several large trials demonstrated radiotherapy reduces local recurrence (approximately halving it) with conflicting impact on survival.[5–7] Evidence that preoperative radiotherapy has superior local control and toxicity profile led to a transition from postoperative to preoperative regimes,[8] with no consensus on whether short-course radiotherapy (SCRT) or long-course chemoradiation (LCCRT) are superior.[9,10]

With increasing survival and radiotherapy use, more patients are at risk from serious long-term radiotherapy-related adverse effects, such as small bowel obstruction (SBO) and gastrointestinal (GI) fistula. Small bowel resection for radiation-related SBO has been shown to be associated with significant morbidity and long-term parenteral nutrition requirement.[11] Most studies focus on survival and oncological outcomes, with late adverse effects often neglected. Several systematic reviews have attempted to quantify patient-reported symptoms, demonstrating higher rates of patient-reported anorectal and sexual dysfunction in patients treated with both radiotherapy and surgery when compared with surgery alone, however the risks of serious complications such as SBO have not been formally or recently assessed.[12–14]

Reviews that have attempted to assess these complications are either methodologically poor, or no longer contemporary (following newer practices such as preoperative radiotherapy). Birgisson *et al*. provided a comprehensive review of late complications of radiotherapy, however, this is now outdated and no meta-analysis was performed,[15] meaning there was no formal assessment of heterogeneity or bias. Chen *et al*. estimated a serious effect prevalence of 8–9%, however, the type of adverse effect was not specified and their meta-analysis included just two studies.[16] Sipaviciute *et al*. attempted to quantify late severe GI morbidity, but included just nine studies with no attempt at meta-analysis.[17] Therefore, there is limited data on the prevalence of serious complications, such as SBO and fistulas, with no previous formal quantification of risks using meta-analysis.

This systematic review and meta-analysis was conducted to quantify the pooled prevalence of long-term serious adverse effects in patients having radiation therapy and surgery for rectal cancer (GI, SBO, GI fistula and genitourinary (GU)), and compare this risk to patients having surgery alone. This crucial information is needed to guide patients when commencing their treatment and health care providers in terms of understanding the longer-term burden likely to fall on both patients and health services.

Materials and methods

Search strategy

The protocol for the review was registered in advance on PROSPERO (ID: CRD42021251605) and conducted in accordance with the PRISMA and MOOSE statements on reporting for systematic reviews.[18,19] A systematic search was constructed around the themes of 'rectal cancer', 'radiotherapy' and 'adverse GI/GU effects', with consultation with an Information Specialist. The search was run on 23 February 2021 using both Ovid Medline and Embase for any English-language study published after 1 January 2000 reporting on the adverse effects of radiation therapy for rectal cancer (Appendix S1). Reference lists from previously published systematic reviews and included studies were hand-searched for additional studies not identified in the search. Results were imported and de-duplicated in Endnote X9 (Clarivate, London).

Study selection criteria

Inclusion criteria: Randomized controlled trials (RCTs), population-based or multi-centre observational studies where adults (≥18 years old) with primary rectal cancer received treatment with both radiotherapy and surgery, reporting on adverse gastrointestinal or genitourinary events >6 months after treatment.

Exclusion criteria: Children (<18 years), re-irradiation of previously irradiated fields, contact radiotherapy/brachytherapy, intraoperative radiotherapy, immunotherapy, experimental treatments such as hyperthermia or proton beam, patients receiving pelvic exenteration (removal of gynaecological/genitourinary organs along with rectum), studies where rectal cancer patients are not reported separately or not reporting site of complication, non-human studies, only acute toxicities reported (<6 months after treatment), patients treated with organ-preservation (radiotherapy +/− local excision alone).

Single-centre observational studies were excluded due to the high risk of bias they may introduce, as were studies with <10 patients receiving radiotherapy for rectal cancer, case series/reports, conference abstracts, systematic reviews. Studies reporting only patient-reported quality of life outcomes, without reporting on severe complications requiring hospital admission/intervention, were excluded (these outcomes have been extensively reported in previous systematic reviews).

Where multiple publications from the same study included the same patient cohort and outcomes at differing time-points, only the publication with the longest follow-up was included to avoid duplication.

Study screening, data extraction and quality assessment

Two blinded reviewers (AM and AR) independently screened titles and abstracts, then full-papers, using Rayyan (Rayyan Systems Inc.[20]). Conflicts were resolved by discussion, or a third reviewer (DJH) if disagreement remained.

Data extraction was completed by both reviewers (AM/AR) independently, with disagreements resolved by discussion. Data were extracted on author, publication year, journal, country, study type, radiotherapy regime, average follow-up duration, number of patients receiving radiotherapy, number in a non-radiotherapy control group if present, definition of late effects, definition of severe effect/grading system used, number of patients with any of the following during follow-up: any severe GI event, SBO, operation for SBO, GI fistula, any severe GU event.

Quality was assessed independently by both reviewers using the Joanna Briggs Institute (JBI) Critical Appraisal Tool for RCTs or cohort studies as appropriate (available from https://jbi.global/critical-appraisal-tools). For observational studies, the cohort study checklist is only appropriate for those with two arms. In single-armed studies, the case-series checklist was more appropriate. One point was awarded if the study fulfilled the criteria for each question in the checklist. This numerical score (out of 13 for RCTs, 11 for the cohort study and 10 for case-series checklists) informs the reader of the quality of the study design and reporting.

Outcome definitions

Primary outcome: Prevalence of severe long-term (>6 months after radiotherapy) GI or GU complications, defined as those requiring hospital admission or intervention.

Those measured using a grading system (e.g., Common Terminology Criteria for Adverse Events (CTCAE),[21] Radiation Therapy Oncology Group (RTOG)[22] or Late Effects Normal Tissues – Subjective, Objective, Management, Analytic (LENT-SOMA)[23]) were defined as severe if they are Grade 3+ (hospital admission/intervention required). Only management scores from LENT-SOMA were used. If no scoring system was used, clinical record, clinician assessment or patient-interview confirming hospital admission or treatment for complication was sufficient for definition of severe.

Secondary outcomes: Individual complications: small bowel obstruction (SBO), enteric fistula.

When a study compared a radiotherapy group against a non-radiotherapy (surgery alone) group, risk ratios were calculated for the increased risk of radiotherapy compared with surgery alone for each outcome above.

Statistical analysis

Meta-analysis was performed for any outcome reported by three or more studies. Analysis was done for combined and individual toxicities. In the case of multiple publications from the same study reporting differing outcomes, the most relevant publication was selected for each outcome. All statistical analysis was performed using Stata SE16 (StataCorp, Texas, USA).

Meta-analysis for toxicity prevalence was performed using the 'metaprop' command. The numerator was the number of patients with the event during follow-up; the denominator was the number at risk in the radiotherapy group. Prevalence values were pooled using the random effects model. The Freeman–Tukey double-arcsine transformation was used to obtain confidence intervals for pooled estimates.[24,25] Heterogeneity was assessed using I^2. Subgroup analysis was carried out to compare results from RCTs and observational studies.

Risk ratios were pooled assuming random effects using the method of DerSimonian and Laird,[26] comparing the risk of the specific event between the radiotherapy and surgery alone groups, with subgroup analysis for RCTs and observational studies.

Results

4044 records were retrieved after de-duplication. After title and abstract screening, 484 were suitable for full-text review. Most were excluded for reporting only acute complications, patient-reported quality of life measures or being single-centre observational studies (PRISMA, Fig. 1). Twenty-four reports from 23 studies met all eligibility criteria and were included in the review; one of these was found from reference lists of included studies. Birgisson published two reports analysing different outcomes from the same study (Swedish Rectal Cancer Trial),[27,28] the

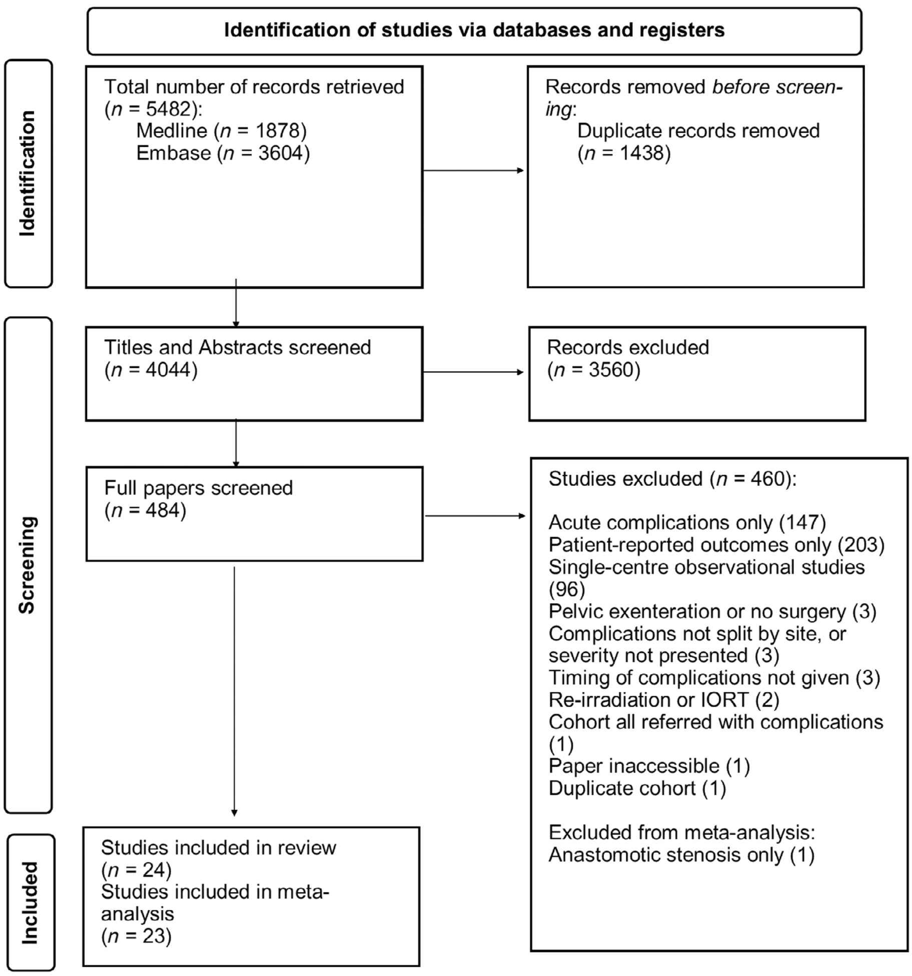


Fig. 1. PRISMA diagram. *Source*: From Reference 18. For more information, visit: http://www.prisma-statement.org/

Table 1 Details of all RCTs included in systematic review

RCTs Author	Year	N (RTx)†	Pre- or postoperative?	Radiotherapy regime	Toxicity grading	Average F/U (months)	Definition of late	Site	JBI (/13)
Azria[46]	2017	584	pre-	LCCRT	NCI/CTC	60	>12 months	GI, GU	10
Birgisson[28]	2005	454	pre-	SCRT	Hospital admissions	Minimum 120	>6 months	GI, GU	10
Birgisson[27]	2008	454	pre-	SCRT versus no RTx	Hospital admissions	Minimum 132	>6 months	GI	10
Bosset[47]	2014	1011	pre-	LCRT versus LCCRT	Surgery	124	>6 months	GI	10
Bosset[48]	2001	229	post-	LCRT versus extended-field (excluded)	Surgery	72	>6 months	GI	10
Bujko[49]	2006	279	pre-	SCRT versus LCCRT	RTOG/EORTC	48	>1 month	GI, GU	10
Cisel[9]	2019	515	pre-	SCCRT versus LCCRT	RTOG/EORTC	84	>1 month	GI, GU	10
Esco[50]	2004	100	post-	LCCRT ± orgotein	RTOG/EORTC	Minimum 12	>3 months	GI, GU	8
Ngan[51]	2012	323	pre-	SCRT versus LCCRT	RTOG/EORTC	71	>6 months	GI, GU	10
Park[52]	2011	220	pre- versus post-	LCCRT	NCI/CTC	52	>2 months	GI, GU	9
Peeters[34]	2005	306	pre-	SCRT versus no RTx	Hospital admissions	60	No minimum	GI, GU	9
Pollack[32]	2006	65	pre-	SCRT versus no RTx	Hospital admissions	180	At follow-up, no minimum set	GI	8
Qin[30]	2016	201	pre-	LCCRT ± oxaliplatin versus no RTx	Intervention	Not stated	>3 months	GI	7
Rodel[53]	2015	1236	pre-	LCCRT ± oxaliplatin	CTCAE	50	>12 months	GI	9
Sauer[8]	2004	799	pre- versus post-	LCCRT	RTOG/EORTC	45.8	>12 months	GI, GU	8
Braendengen[31]	2011	77	pre-	LCCRT versus LCRT	Hospital admissions	81	Not defined but minimum 4 year follow-up	GI	9

†Number of patients in the radiotherapy group. F/U, follow-up; GI, gastrointestinal; GU, genitourinary; JBI, Joanna Briggs Institute score; LCCRT, long-course chemoradiation; LCRT, long-course radiotherapy; no RTx, no radiotherapy group; SCRT, short-course radiotherapy.

2005 publication reported all combined GI/GU outcomes and the 2008 publication reported specific complications, therefore both were included. A total of 15 438 unique patients were included (Tables 1 and 2).

Of the 24 reports, 23 were suitable for meta-analysis. One (Egenvall, 2014[29]) provided additional data to allow analysis after correspondence with the author. Qin *et al*. was excluded from the meta-analysis as the only outcome reported was anastomotic stenosis, which was not analysed in this review.[30]

Radiotherapy regimens given were predominantly long-course (14), short-course (3), a comparison of both (3), or both together (3). Long-course radiotherapy was predominantly 50Gy, and short-course 25Gy, with radiotherapy delivered predominantly by 3 or 4 field 'box' techniques. All patients having LCCRT also had treatment with 5-FU or capecitabine, mostly 5-FU. The grading system for complications was: CTCAE or NCI/CTC (7), RTOG/EORTC (6), hospital admission (6) and need for intervention/surgery (4).

Quality

All studies scored highly on JBI score (Tables 1 and 2). No RCT scored the maximum as three points are awarded for blinding, which is challenging to achieve in a radiotherapy trial. 8 (50%) of RCTs scored 10/13, 7 (44%) scored 8–9 and the only study scoring less (Qin) was not included in the meta-analysis as it only reported on anastomotic stenosis.[30] Three observational studies were assessed using the cohort studies checklist, five using the case-series checklist. All studies scored the maximum score or one less.

All gastrointestinal ($n = 21$)

Fourteen RCTs and seven observational studies reported data on all GI complications. Average follow-up across studies was 60 months (range 18 to 180), encompassing 8469 patients. There was a wide range in the reported prevalence of severe GI complications, 3.0–34.6%.

All 21 studies were suitable for meta-analysis. The pooled prevalence from these studies was 11% (95% confidence interval (95% CI) 8–14%) for GI complications requiring hospital admission or treatment after radiotherapy treatment and surgery for rectal cancer (Fig. 2). Heterogeneity was high (I^2 96%). Three studies reported much higher prevalence (Birgisson, Pollack, Braendengen[28,31,32]). Removing these did little to change heterogeneity (I^2 95%), although the pooled prevalence decreased to 8% (95% CI 6–11%).

Five studies compared a radiotherapy with non-radiotherapy control group. However, four of these only reported on SBO.[29,32–34] Therefore, a comparison was not done for all GI complications.

Small bowel obstruction ($n = 13$)

Nine RCTs and four observational studies reported on the incidence of late SBO, encompassing 6947 patients. Eight reported on SBO requiring operation. There was a wide variation in the reported prevalence of SBO, 1.1–29.2%, and SBO that required an operation, 1.6–13.0%.

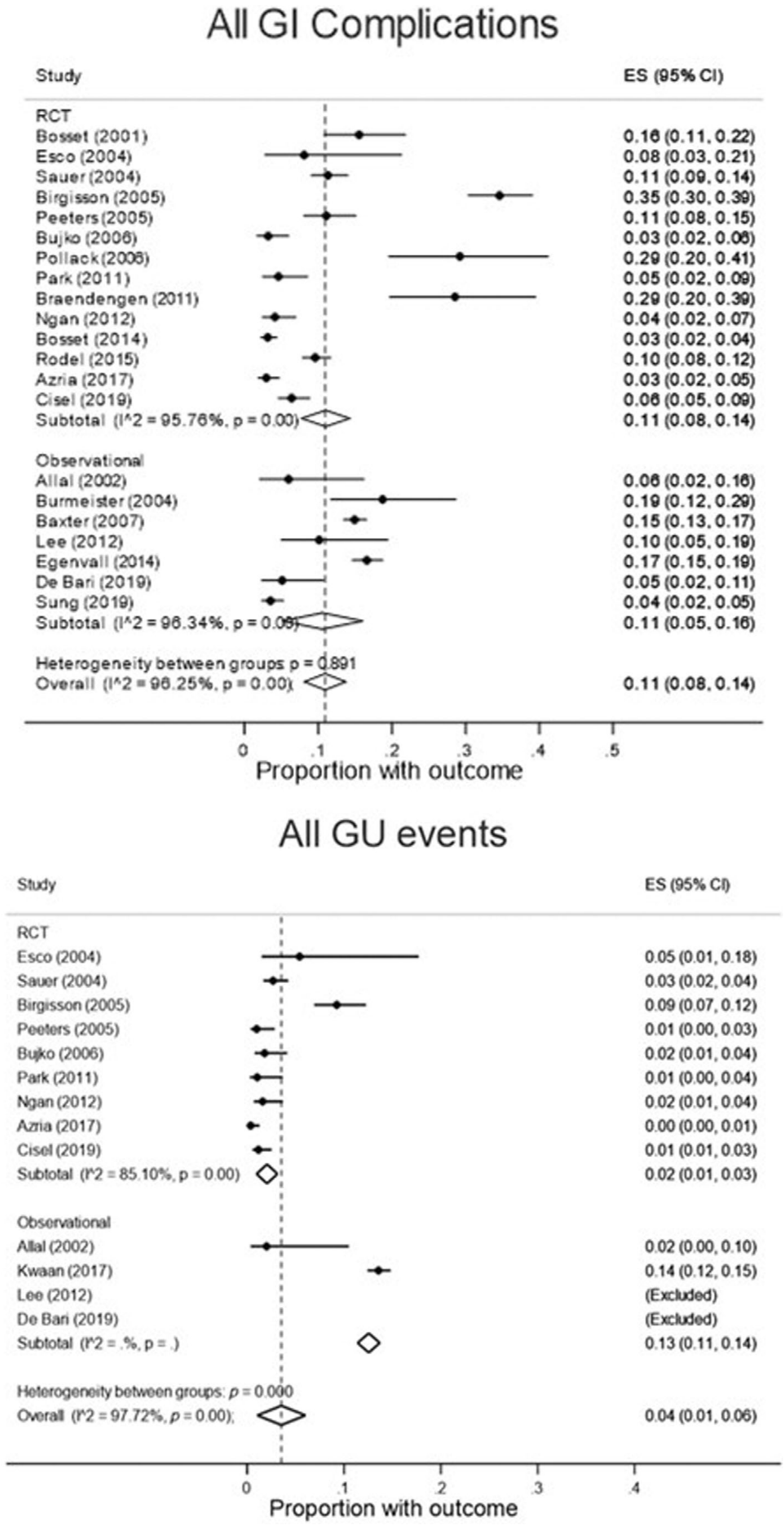
All 13 studies were included in the meta-analysis. Pooled prevalence for SBO after radiotherapy treatment and surgery was 9% (95% CI 6–12%, I^2 98%; Fig. 3). Pollack and Braendengen[31,32] were outliers: prevalence 29% and 22%, respectively. Subgroup analysis showed that prevalence was higher in observational studies

Table 2 Details of all observational studies included in systematic review

Author	Year	Design	N (RTx)†	Pre- or postoperative?	Radiotherapy regime	Toxicity grading	Average F/U (months)	Definition of late	Site	JBI‡
Observational studies										
Allal[54]	2002	Prospective Cohort	50	pre-	LCRT	RTOG/EORTC	32	>3 months	GI, GU	10/10
Baxter[33]	2007	Retrospective Population-based	1994	Both and control	Any RTx versus no RTx	Hospital admissions	42	No minimum	GI	10/11
Burmeister[55]	2004	Prospective Cohort	80	post-	LCCRT	LENT/SOMA, surgery	84	Not defined	GI	9/10
De Bari[36]	2019	Retrospective Cohort	117	pre-	LCCRT + boost	CTCAE	45	>3 months	GI, GU	10/10
Kwaan[35]	2017	Retrospective Population-based	4842	Both and control	Any RTx versus no RTx	CTCAE	32	Not defined	GU	10/11
Lee[37]	2012	Prospective Cohort	69	pre-	LCCRT + boost	CTCAE	69	Not defined	GI, GU	9/10
Sung[56]	2019	Retrospective Cohort	620	Pre-	LCCRT	CTCAE	43	Not defined	GI	11/11
Egenvall[29]	2014	Retrospective Cohort	1267	Both	Any RTx	Hospital admissions, surgery	Minimum 60	>1 month	GI	10/10

†Number of patients in the radiotherapy group. ‡Joanna Briggs Institute score – the cohort study checklist was used if appropriate and scored out of 11, otherwise the case-series checklist was used, scored out of 10. F/U, follow-up; GI, gastrointestinal; GU, genitourinary; JBI, Joanna Briggs Institute score; LCCRT, long-course chemoradiation; LCRT, long-course radiotherapy; no RTx, no radiotherapy group; SCRT, short-course radiotherapy.

Fig. 2. Proportion of patients with each complication (primary outcome).



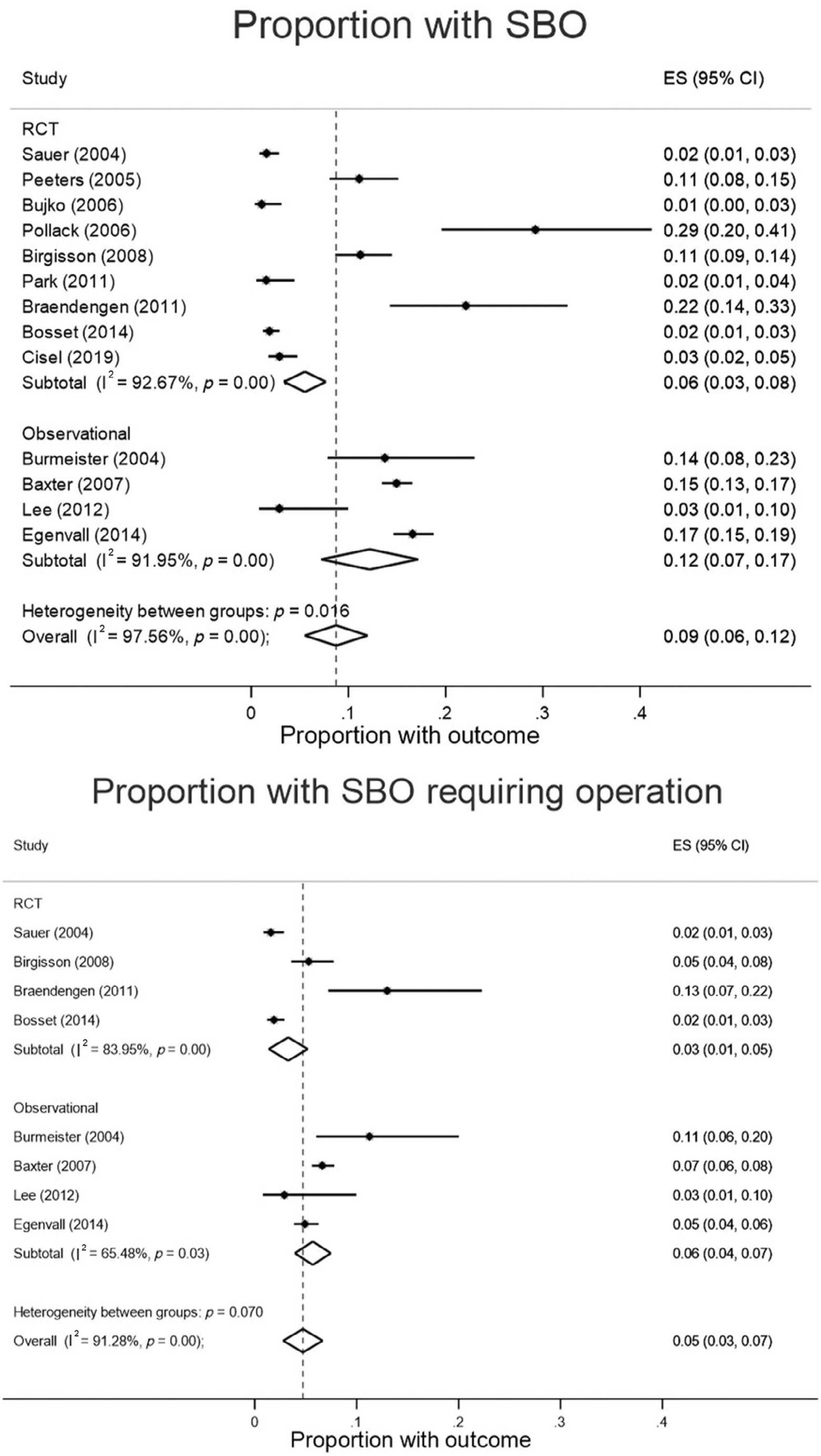


Fig. 3. Prevalence of small bowel obstruction (secondary outcome).

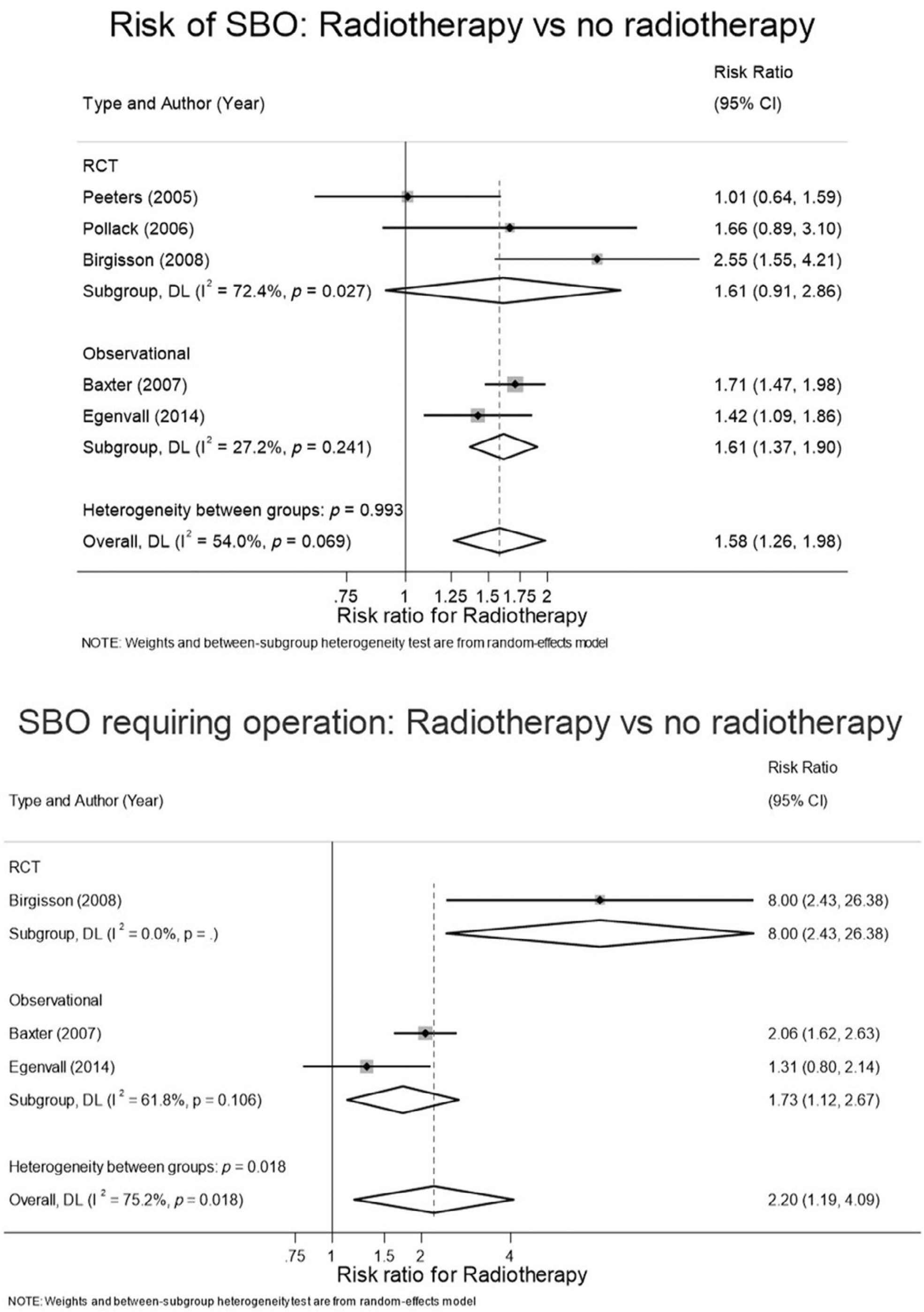


Fig. 4. Risk of SBO in those receiving radiotherapy and surgery versus surgery alone (secondary outcome).

(12%, 95% CI 7–17%) compared to RCTs (6%, 95% CI 3–8%). For SBO requiring operation, the prevalence was 5% (95% CI 3–7%, I^2 91%); 3% in RCTs (95% CI 1–5%) and 6% in observational studies (95% CI 4–7%; Fig. 3).

Five studies reported on SBO in a radiotherapy and surgery group versus a surgery-alone control group.[27,29,32–34] Radiotherapy showed a 58% increased risk on meta-analysis when compared to surgery alone (RR 1.58, 95% CI 1.26–1.98, I^2 54%; Figure 4). Subgroup analysis for RCTs showed a similar point estimate but less precision (RR 1.61, 95% CI 0.91–2.86).

Three studies looked at whether radiotherapy was associated with an increased risk of operative intervention for SBO compared with surgery alone, showing a twofold increased risk (RR 2.20, 95% CI 1.19–4.09, I^2 75%, Fig. 4).

Gastrointestinal fistula ($n = 7$)

Seven studies (5 RCTs, 2 observational) reported on the long-term prevalence of GI fistulas. The reported prevalence varied from 0.9% to 6.5%.

Meta-analysis showed a prevalence of 1% (95% CI 1–2%, I^2 26%; Fig. S1). Only one study had a non-radiotherapy control group (Birgisson[27]), which showed no increase in fistulas in those who had radiotherapy treatment (RR 1.22, CI 0.46–3.22), however, numbers were small.

Genitourinary ($n = 13$)

Thirteen studies reported on the prevalence of long-term GU complications, average follow-up 57 months (range 18–120), encompassing 6652 patients. Reported prevalence varied from 0% to 13.6%. The highest prevalence was seen in Kwaan *et al.*,[35] which made up almost half of the GU cohort (3112 patients). This was a population-based observational study using Surveillance Epidemiology and End Results-Medicare data (SEER), with the outcome defined as a urinary diagnosis with associated procedure (correlating to Grade 3–4 in the CTCAE). This study reported outcomes at multiple time-points, and reported increasing cumulative incidence over time (14.2% at 2 years, 20.6% at 5 years and 27.6% at 10 years in the preoperative radiotherapy group). The number of patients in the cohort was not reported at 5 years and only 11 remained at 10 years, therefore the 2 year time-point was used. Two studies reported no GU complications (117 and 69 patients respectively[36,37]) so contributed no information to the meta-analysis.

Eleven studies were suitable for meta-analysis. Overall prevalence for any GU complication was 4% (95% CI 1–6%, Fig. 2). This differed between RCTs (2%, 95% CI 1–3%) and observational studies (13%, 95% CI 11–14%) on subgroup analysis, influenced by Kwaan *et al*.[35] Heterogeneity was very high ($I^2 = 98\%$).

Three studies compared the risk of serious GU events in a radiotherapy group against a surgery-alone group (Fig. S2), demonstrating no increase in risk (RR 1.10, CI 0.88–1.38, I^2 25%).

Discussion

Key findings

This review demonstrates that radiotherapy treatment for rectal cancer is associated with an important burden of serious long-term GI and GU events requiring hospital admission or treatment. Overall, there is a large variation in the prevalence of outcomes and high heterogeneity, reflecting differing populations and time-periods studied. At an average follow-up of 60 months, the estimated prevalence of a long-term GI complication of their radiotherapy treatment requiring hospital admission or intervention averaged over all populations was 11%. The equivalent values were 4% for a serious GU event; 9% for hospitalization with small bowel obstruction, and 5% for having a second operation to manage their SBO, a large number of those undergoing radiotherapy treatment. These results show that for SBO, the risk is 58% higher among those having radiotherapy than patients undergoing surgery alone.

It is worth noting that three studies showed a much higher prevalence of GI complications,[28,31,32] with two of these also much higher for SBO.[31,32] This may be explained by the fact these studies had some of the longest follow-up time of all the studies; the longer the follow-up the higher chance a patient suffers a complication. This demonstrates an ongoing effect of radiotherapy that can lead to adverse effects appearing many years after treatment. This is collaborated by Kwaan *et al*., showing an increase in cumulative incidence at later time points.[35]

Organ-preservation (radiotherapy ± local excision) was not studied in this review as it would add further heterogeneity to the results and there is still limited long-term follow-up data reporting toxicities on this relatively novel treatment. This is an area that would benefit from further research as the data becomes available, as the impact of radiotherapy here is still an unknown.

Strengths and limitations

This systematic review and meta-analysis has several strengths. A large cohort of patients was included after a large number of studies were screened, with a median follow-up time of 5 years. These results add to the existing literature by estimating a pooled prevalence of late severe GI and GU effects by meta-analysis for the first time, combining RCTs and multicentre observational studies. As the reported prevalence of adverse effects varies greatly between studies, combining the results allows us to get a truer idea of the proportion of patients affected. By using clearly defined, objective outcomes, a meta-analysis has been performed where other reviews have failed due to high heterogeneity in outcome reporting.

There are several limitations. There was a large amount of heterogeneity between studies in terms of design, radiotherapy regime and outcome measurement tool. High levels of heterogeneity are expected when pooling descriptive measures such as prevalence. This was mitigated by excluding single-centre observational studies, to reduce risk of bias, and using an objective outcome definition that translates easily between different grading tools or assessment methods. Random effects meta-analysis was chosen to account for the high heterogeneity and the assumption that prevalence will differ between populations. Subgroup analysis was done by study type due to the higher prevalence of outcomes in observational studies, to provide greater transparency in outcome reporting. Both SCRT and LCCRT are used globally; a previous review did not show a difference in late toxicity between the two regimes,[16] so they have been combined here. Only patients who had resectional surgery were included, to reduce heterogeneity that local excision or watch-and-wait patients may have on the data, but these treatment pathways merit assessment.

Although only two databases were searched, a large number of studies were retrieved and reference lists searched, including more studies than previous reviews. Another limitation was the varied definition of a 'late' toxicity, varying from 1 month to 1 year after treatment. The median follow-up was long enough and acute complications excluded to minimize impact on the results. It is also possible that patients having radiotherapy treatment were selected because they had more advanced disease. However, RCTs did not allocate patients based off disease stage or have a significant difference in disease stage between groups. Subgroup analysis was done to account for the impact this may have when including observational studies. Baxter *et al*., which showed a higher SBO rate, had a large proportion of patients receiving postoperative radiotherapy (73.6%).[33] Subgroup analysis for preoperative radiotherapy alone did not show a significant increase in SBO compared to surgery alone. However, the number of patients and follow-up duration for this group was much smaller, reducing power and event rate, which could account for this. However, results may be less applicable to preoperative-only regimes.

The lack of a standard definition of severe or late toxicities increases heterogeneity of outcomes between studies. A standardized definition, developed by consensus, would reduce this to allow the evidence base to build more effectively.

Results in context of previous work

Most previous systematic reviews have focussed on patient-reported functional outcomes,[12–15] without estimating requirement of hospital treatment for complications such as SBO or fistula, or the additive risk over surgery alone. Where reviews have tried to quantify this, they have been limited by a small number of studies with no meta-analysis,[17] or not reporting site of toxicity.[10,14,16]

The prevalence of severe GI effects in this meta-analysis (9%) is in keeping with previously published literature.[15,17] Birgisson's systematic review described a prevalence of SBO after radiotherapy of 11–13%, with a potentially reduced risk (9%) seen in preoperative radiotherapy when compared with postoperative.[15] The studies included in this review are more contemporary, with increased use of preoperative radiotherapy and laparoscopic surgery, so therefore reflect current practice. Prevalence of GI fistulation after pelvic radiotherapy is poorly described in the literature, likely due to its rarity. The prevalence estimated here attempts to counteract the lack of power small studies have for this rare outcome.

The estimated prevalence of severe GU effects, 4%, is in keeping with Birgisson's review.[15] GU effects, especially those requiring hospitalization, are much less commonly reported in the literature than GI. GU events reported vary, from urinary catheterisation through to major operative intervention, which adds to the heterogeneity seen. Kwaan *et al.*, the biggest study looking at adverse urinary events as a primary outcome estimates a prevalence much higher than any other study.[35] Interestingly, this is the only study to show a significantly higher risk in those undergoing radiotherapy. This increased prevalence could be explained by a high proportion of postoperative radiotherapy patients. The population-based observational nature also means that patients presenting to other hospitals with complications are not missed, which may be the case in long-term follow-up of RCTs. The objective measurement of procedure codes as an outcome means this study is unlikely to over-report results. This may suggest that serious urinary adverse effects are under-reported in trials.

Clinical significance and implications for the future

Radiotherapy treatment is important in reducing the risk of local recurrence in rectal cancer (T3, T4 and node positive),[6,7] but the high proportion of patients suffering long-term complications should be discussed prior to commencing treatment, as $\sim$1 in 10 will require hospitalization for a serious GI effect or SBO, and 1 in 20 re-operation for SBO. Efforts should be taken preoperatively to mitigate damage and manage symptoms. Novel radiotherapy techniques have been developed to limit the dose received by the small bowel,[38,39] and hyperbaric oxygen therapy has been postulated as a treatment for late radiation-associated injury, with a possible effect seen for proctitis and cystitis but with low evidence.[40–42] The set-up of speciality 'late-effects' gastroenterology clinics for the consequences of pelvic radiation has been shown to be successful in reducing symptoms in gynaecological cancer patients[43] and has been recommended to be establizhed,[44] although the effect this may have on SBO is unclear. The increasing use of laparoscopic surgery for rectal cancer may be beneficial in reducing the prevalence of SBO in the long-term.[45] With a move towards some patients being treated with (chemo)radiotherapy and organ-preservation/local excision for early rectal cancer, there is still potentially a large radiotherapy effect on long-term complications which requires further assessment once more long-term data are available.

A focus on earlier and lower stage, diagnosis of rectal cancer would reduce the burden of complications by reducing the need for radiotherapy treatment as more patients could be treated by surgery alone.

Conflict of interest

None declared.

Author contributions

Alastair J. Morton: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; visualization; writing – original draft; writing – review and editing. **Adil Rashid:** Data curation; formal analysis; investigation; methodology; resources; software; writing – review and editing. **Joanna S. C. Shim:** Conceptualization; data curation; formal analysis; investigation; methodology; software; validation; writing – review and editing. **Joe West:** Conceptualization; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – review and editing. **David J. Humes:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; visualization; writing – review and editing. **Matthew J. Grainge:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – review and editing.

Ethics approval

Protocol registered on PROSPERO (CRD42021251605).

Data availability statement

No individualized patient data, data are available on request.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Supporting Information

Supplementary Figure S1. Prevalence of GI fistulas in those receiving radiotherapy

Supplementary Figure S2. GU events in those subjected to radiotherapy compared to surgery alone

Appendix – Search Strategy

Medline: 1864 results

1. rectal cancer.mp. or Rectal Neoplasms/

2. ((rectum adj3 cancer) or (rectum adj3 carcinoma) or (rectum adj3 adenocarcinoma)).mp.

3. (rectal cancer* or rectal carcinoma* or rectal adenocarcinoma*).mp.

4. radiotherapy.tw. or exp Radiotherapy/

5. Neoadjuvant Therapy/

6. Chemoradiotherapy, Adjuvant/ or Radiotherapy, Adjuvant/

7. (radiation or irradiation or radio?chemotherapy or chemo?radiation or chemo?radiotherapy).tw.

8. exp Chemoradiotherapy/

9. Radiation Oncology/

10. neo?adjuvant.tw.

11. ((adverse adj2 event*) or (adverse adj2 effect*) or (adverse adj2 reaction*) or (adverse adj2 outcome*)).tw.

12. toxic*.tw.

13. (function or dysfunction).tw.

14. (CTCAE or NCI?CTC or RTOG or EORTC).mp.

15. "Quality of Life"/

16. (f?ecal incontinence or proctitis or proctopathy).mp.

17. Diarrhea/ or Constipation/

18. (anorectal function or anorectal dysfunction or diarrh?ea).mp.

19. obstruction.mp. or exp Intestinal Obstruction/

20. exp Urinary Incontinence/ or incontinence.mp. or exp Fecal Incontinence/

21. (urinary or genito?urinary).tw. or exp Urinary Bladder Diseases/

22. exp Cystitis/ or cystitis.mp.

23. exp Sexual Dysfunction, Physiological/ or Sexual Health/ or sexual.mp.

24. Erectile Dysfunction/ or erectile.mp. or impoten*.mp.

25. ((side adj1 effect*) or (undesirable adj1 effect*) or (unintended adj1 effect*) or (unintended adj1 event*)).tw.

26. (tolera* or harm* or safe*).tw.

27. (case report* or case series or case study).tw.

28. letter/

29. historical article/

30. 27 or 28 or 29

31. 1 or 2 or 3

32. 4 or 5 or 6 or 7 or 8 or 9 or 10

33. 11 or 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

34. 31 and 32 and 33

35. 34 not 30

36. limit 35 to (english language and humans and yr="2000 -Current" and "all adult (19 plus years)")

Embase: 3562 results

1. exp rectum cancer/

2. (rectal cancer or rectum cancer).tw.

3. ((rect* adj3 adenocarcinoma) or (rect* adj3 carcinoma) or (rect* adj3 cancer)).tw.

4. radiotherapy.tw. or exp radiotherapy/

5. neoadjuvant therapy/ or neo?adjuvant.tw.

6. exp adjuvant chemoradiotherapy/ or exp chemoradiotherapy/

7. (radiation or irradiation or radio?chemotherapy or chemo?radiation or chemo?radiotherapy).tw.

8. radiation oncology/

9. ((adverse adj2 event*) or (adverse adj2 effect*) or (adverse adj2 outcome*) or (adverse adj2 reaction*)).tw.

10. toxic*.tw.

11. (function* or dysfunction*).tw.

12. patient-reported outcome/

13. (CTCAE or NCI?CTC or RTOG or EORTC).mp.

14. "quality of life"/

15. exp feces incontinence/

16. diarrhea/

17. (diarrh?ea or constipation or obstruction or incontinence).tw.

18. constipation/

19. exp intestine obstruction/

20. incontinence/ or urine incontinence/

21. bladder function/

22. cystitis.mp. or cystitis/

23. sexual.mp. or sexual health/ or sexual dysfunction/

24. erectile dysfunction/ or impotence/ or erectile.mp.

25. ((side adj1 effect*) or (unintended adj1 effect*) or (unintended adj1 event*) or (undesirable adj1 effect*)).tw.

26. 1 or 2 or 3

27. 4 or 5 or 6 or 7 or 8

28. 9 or 10 or 11 or 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

29. 26 and 27 and 28

30. case study/

31. case report*.tw.

32. abstract report/ or letter/

33. conference proceeding.pt.

34. conference abstract.pt.

35. editorial.pt.

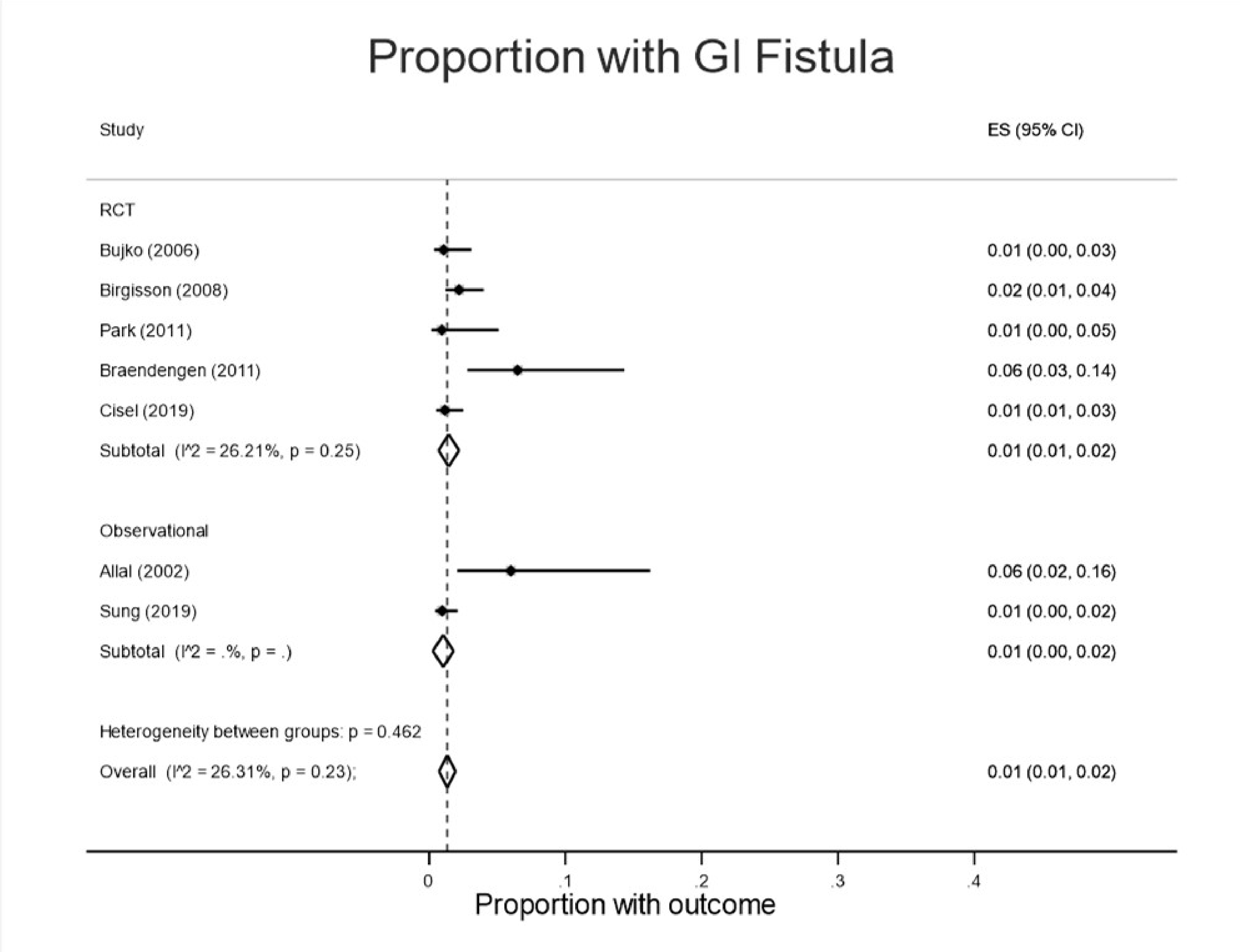
36. letter.pt.

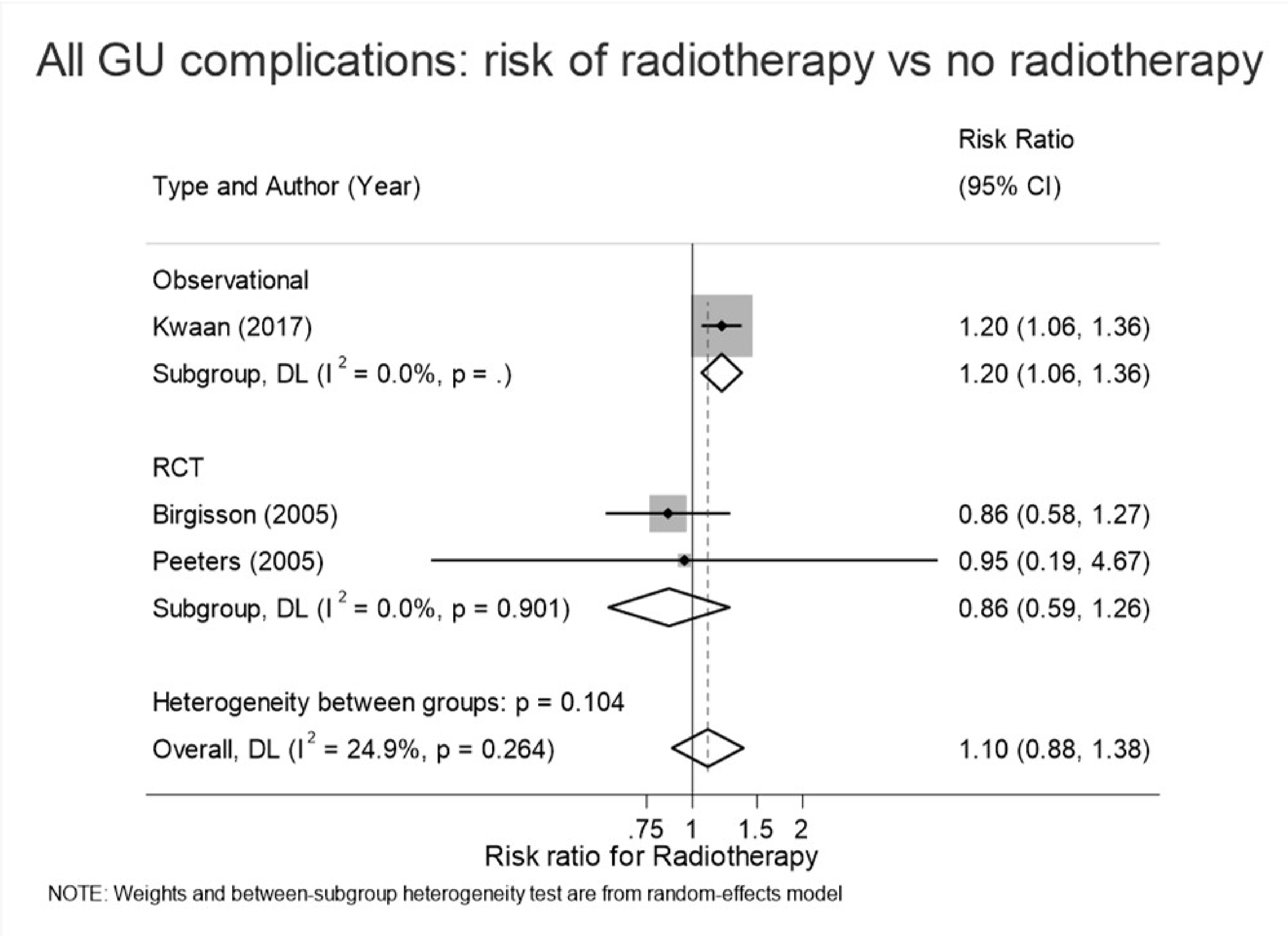
37. note.pt.

38. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37

39. 29 not 38

40. limit 39 to (human and english language and yr="2000 -Current" and (adult <18 to 64 years> or aged <65+ years>))


Proportion with GI Fistula
Study
ES (95% CI)
RCT
Bujko (2006)
0.01 (0.00, 0.03)
Birgisson (2008)
0.02 (0.01, 0.04)
Park (2011)
0.01 (0.00, 0.05)
Braendengen (2011)
0.06 (0.03, 0.14)
Cisel (2019)
0.01 (0.01, 0.03)
Subtotal (I^2 = 26.21%, p = 0.25)
0.01 (0.01, 0.02)
Observational
Allal (2002)
0.06 (0.02, 0.16)
Sung (2019)
0.01 (0.00, 0.02)
Subtotal (I^2 = .%, p = .)
0.01 (0.00, 0.02)
Heterogeneity between groups: p = 0.462
Overall (I^2 = 26.31%, p = 0.23);
0.01 (0.01, 0.02)
0
.1
.2
.3
.4
Proportion with outcome



All GU complications: risk of radiotherapy vs no radiotherapy
Risk Ratio
Type and Author (Year)
(95% CI)
Observational
Kwaan (2017)
1.20 (1.06, 1.36)
Subgroup, DL (I 2 = 0.0%, p = .)
1.20 (1.06, 1.36)
RCT
Birgisson (2005)
0.86 (0.58, 1.27)
Peeters (2005)
0.95 (0.19, 4.67)
Subgroup, DL (I 2 = 0.0%, p = 0.901)
0.86 (0.59, 1.26)
Heterogeneity between groups: p = 0.104
Overall, DL (I 2 = 24.9%, p = 0.264)
1.10 (0.88, 1.38)
.75
1
1.5
2
Risk ratio for Radiotherapy
NOTE: Weights and between-subgroup heterogeneity test are from random-effects model