


Effects of Preoperative Radiotherapy on Long-Term Bowel Function in Patients With Rectal Cancer Treated With Anterior Resection: A Systematic Review and Meta-analysis

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Abstract

Background: Anterior resection is a common surgical approach used in rectal cancer surgery; however, this procedure is known to cause bowel injury and dysfunction. Neoadjuvant therapy is widely used in patients with locally advanced rectal cancer. In this study, we determined the effect of preoperative radiotherapy on long-term bowel function in patients who underwent anterior resection for treatment of rectal cancer. **Methods:** We performed a comprehensive literature search of the PubMed, Embase, Web of Science, and the Cochrane Library databases. A random-effects model was used in the meta-analysis by the Review Manager software, version 5.3. **Results:** This systematic review and meta-analysis included 12 studies, which used low anterior resection syndrome score with a total of 2349 patients. Based on them, we concluded that low anterior resection syndrome was significantly more common in the preoperative radiotherapy group (odds ratio 3.59, 95% confidence interval 2.68–4.81, $P < .00001$) and that major low anterior resection syndrome also occurred significantly more frequently in the preoperative radiotherapy group (odds ratio 3.28, 95% confidence interval 2.05–5.26, $P < .00001$). Subgroup analyses of long-course radiation, total mesorectal excision, and non-metastatic tumors were performed, and the results met the conclusions of the primary outcomes. **Conclusions:** Preoperative radiotherapy negatively affects long-term bowel function in patients who undergo anterior resection for rectal cancer.

Keywords

preoperative radiotherapy, neoadjuvant radiotherapy, rectal cancer, bowel function, anterior resection, low anterior resection syndrome

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Abbreviations

AR, anterior resection; CI, confidence interval; LARC, locally advanced rectal cancer; LARS, low anterior resection syndrome; nCRT, neoadjuvant chemoradiotherapy; NOS, Newcastle-Ottawa scale; NRCT, non-randomized controlled trial; OR, odds ratio; PME, partial mesorectal excision; QOL, quality of life; RCT, randomized controlled trial; TME, total mesorectal excision; UICC, Union for International Cancer Control.

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Introduction

Anterior resection (AR) is the classical and most common surgical approach used for rectal cancer surgery. Following advances in surgical concepts and techniques, currently, many hospitals perform AR even for low rectal cancer close to the anus. Although AR is a useful sphincter-preserving approach for the management of patients with rectal cancer, it is also associated with the risk of postoperative bowel dysfunction including incontinence and constipation, among other such adverse effects, which negatively and significantly affect patients' quality of life (QOL). These symptoms are collectively referred to as low anterior resection syndrome (LARS), with a reported prevalence rate as high as 60% to 90%.¹⁻⁶

The National Comprehensive Cancer Network and European Society for Medical Oncology guidelines recommend preoperative concurrent chemoradiotherapy as the preferred standard treatment for locally advanced rectal cancer (LARC). Administration of neoadjuvant chemoradiotherapy (nCRT) leads to tumor shrinkage or phase reduction, and a consequent increase in the complete resection rates and reduced local recurrence rates.⁷ Previous studies have focused merely on perineal or systemic reactions secondary to radiation and drugs as adverse effects of nCRT, but the effects on postoperative bowel function were usually overlooked.⁷ In recent years, several meta-analyses have reviewed the prevalence and risk factors of LARS.^{3,8-10} However, only a few reviews have focused on the effects of nCRT.¹¹ Therefore, we performed this systematic review and meta-analysis of the existing literature to determine the effects of preoperative radiotherapy on long-term bowel function in patients who underwent AR for rectal cancer.

Material and Methods

Study Selection

These systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.¹² The study was registered before analysis at the International Prospective Register of Systematic Reviews. We performed a comprehensive literature search of the PubMed, Embase, Web of Science, and the Cochrane Library databases between 2012 and March 2022, since the LARS score was introduced from then. Studies included randomized controlled trials (RCTs) and non-RCTs (NRCTs) if available. For better understanding, Supplementary Tables 1 to 4 would show the complete search strategy.

Following were the inclusion criteria for this study: (a) reports that described patients diagnosed with rectal cancer, (b) those

that described AR as the surgical approach, (c) studies in which AR was performed with or without preoperative radiotherapy, and (d) studies that reported the LARS score for postoperative bowel function evaluation. Exclusion criteria were as follows: (a) letters, reviews, case reports, expert opinions, or only protocols, (b) AR performed for noncancerous lesions or colon cancer, (c) local excision, endoscopic resection, or intersphincteric resection, (d) data mixed with postoperative radiotherapy, (e) bowel function evaluation based on other scales and, (f) non-English publications.

Two reviewers (ZL and ZZ) independently screened the titles and abstracts, and we subsequently scrutinized the complete texts of the selected articles and the relevant references. Disagreements were resolved through discussion between the 2 reviewers; a third author (XY) was consulted for consensus-based resolution. Moreover, we attempted to contact the authors of conference abstracts or articles with missing data.

Types of Outcomes

Comparison of the LARS score in patients who underwent AR for rectal cancer with and without preoperative radiotherapy was the primary outcome in this study. Secondary outcomes were subgroup analysis of long-course radiation, total mesorectal excision (TME), and nonmetastatic tumors, with the same indicators as the primary outcome.

Data Collection and Quality Assessment

Data were independently extracted by 2 reviewers (ZL and ZZ), and variables recorded included year, country, study design, number of participants, age, sex, Union for International Cancer Control (UICC) tumor stage, tumor height, follow-up duration, preoperative radiotherapy rate, course of radiation, and temporary diverting stoma. Disagreements were resolved through discussion between the 2 reviewers; a third author (XY) was consulted for consensus-based resolution.

All studies included in this research were NRCTs or secondary RCTs that were not performed following the principles of RCTs; therefore, we uniformly utilized the Newcastle-Ottawa scale (NOS)¹³ with a total of 9 points used to assess the risk of bias. NRCTs with NOS scores ≥ 5 points were considered high-quality studies and were therefore eligible for analysis.

Statistical Analysis

Basic descriptive statistical methods were used to summarize patient characteristics and outcome data. A systematic review and

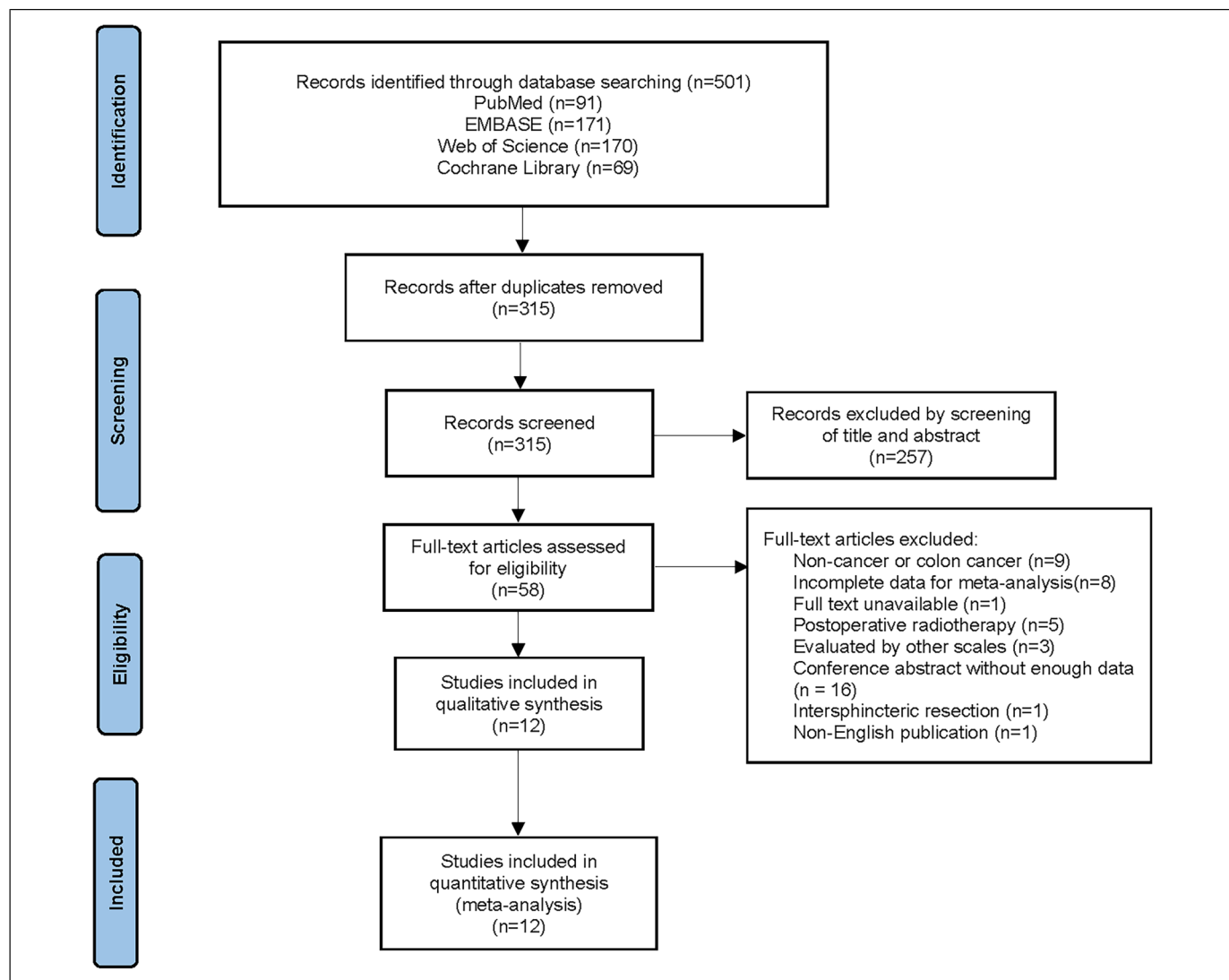


Figure 1. PRISMA selection flow diagram.

meta-analysis were performed following the accumulation of sufficient research data. We performed random-effects meta-analysis using the Review Manager software, version 5.3 (<https://community.cochrane.org/help/tools-and-software/revman-5>), and the Mantel-Haenszel method was used to calculate the odds ratio (OR). The outcomes are expressed as forest plots with ORs and 95% confidence intervals (CIs). Heterogeneity was confirmed using I^2 and χ^2 statistics. Sensitivity analysis was performed in cases of significant heterogeneity.

Results

Study Selection and Quality Assessment

Our literature search yielded 501 articles; 315 studies were identified after discarding duplicates. After the exclusion of irrelevant articles, 58 studies were available for full-text review. Eventually, 12 studies¹⁴⁻²⁵ with 2349 patients who underwent evaluation of the LARS score were included in the

quantitative synthesis (Figure 1). NOS was used for quality assessment, and Supplementary Table 5 and Supplementary Figure 1 show the methodological quality and risk of bias.

Bowel Function Assessment

Patient characteristics. The 12 studies included 2 cross-sectional, 8 cohort, and 2 secondary-analysis RCT studies. Their baseline patient characteristics are shown in Table 1. Among studies whose data were available, the median age was 60 to 70 years. The UICC tumor stage ranged from stage I to IV, including cases of complete remission. All patients in whom AR was performed underwent first- or second-stage anastomosis owing to administration of temporary diverting stoma. Five studies reported TME in 100% of patients, and 4 studies reported both TME and partial mesorectal excision (PME); 2 articles were unclear. Notably, temporary diverting stomas were created in most patients. The interval between the restoration of intestinal continuity and follow-up was at least 12 months, except for the

Table 1. Baseline Characteristics of Studies With LARS Score Assessment.

Study	Design	Number of participants	Median age (range), years old	Tumor stage (UICC)	Tumor height, cm	Number of male (%)	Number of preoperative radiotherapy (%)	Preoperative radiotherapy course	Mesorectal treatment	Temporary diverting stoma (%)	Median follow-up time (range), months	Bowel dysfunction due to preoperative radiotherapy
Bregendahl, Denmark, 2013	Cross-sectional study Multi-center	938	64 (34-92)	I II III UK	0-5 5-10 >10 UK	536 (57)	191 (20)	Long course Short course	TME PME	513 (55)	54 (25-97)	Yes ^a
Emmertsen, Denmark, 2013	Prospective study Multi-center	183	66 (37-87)	I II III	0-5 5-10 10-15	NA	31 (17)	NA	TME PME	NA	12	Yes ^a
Bondeven, Denmark, 2015	Prospective study Multi-center	125	64 (39-84)	I II III	0-5 5-10 10-15	79 (63)	25 (20)	Long course	TME PME	84 (67)	18 (12-24)	Yes ^a
Qin, China, 2017	Cross-sectional study Single-center	142	NA	II III	0-5 5-10 10-15	91 (64)	88 (62)	Long course	TME	117 (82)	19 (12-37)	Yes ^a
Sturiale, Italy, 2017	Retrospective study Multi-center	93	66 (29-83)	I II III	0-5 5-9.9 10-12	58 (62)	41 (44)	Long course	TME	54 (58)	5.5 (4.4-7.2)	Yes ^a
Croese, Australia, 2018	Retrospective study Single-center	64	64.5 (54.2-71.7) ^b	I II III	0-5 5-10 10-15	40 (63)	21 (33)	Long course Short course	NA	42 (66)	44 (12-135)	Yes
Sun, China, 2019	Secondary analysis of RCT	220	56 (27-77)	II III	0-5 5-10 >10	145 (66)	132 (60)	Long course	TME	170 (77)	37.1 (23.1-87.3)	Yes ^a
Bohlok, Belgium, 2019	Prospective study Single-center	43	62 ^c	I II III NA	Low Middle	23 (53)	39 (91)	Long course	TME	41 (95)	71 (30-133)	No
D'Alba, Italy, 2020	Prospective study Single-center	26	65 (2) ^c	NA	NA	12 (46)	17 (65)	NA	NA	NA	21 (12-36)	Yes
Sandberg, Sweden, 2020	Prospective study Multi-center	386	NA	I II III IV	NA	219 (56)	176 (46)	NA	NA	300 (78)	12 or 24	Yes
Theodoropoulos, Greece, 2020	Prospective study Single-center	78	NA	I II III	<7 7-12 12-15	56 (72)	20 (26)	Long course	TME PME	48 (62)	24	Yes
Dulskas, Lithuania, 2021	Secondary analysis of RCT Multi-center	51	61 ^c	I II III IV	4 (1.56) ^c	25 (49)	27 (53)	NA	TME	51 (100)	36 (17-97)	No

Abbreviations: LARS, low anterior resection syndrome; UICC, Union for International Cancer Control; TME, total mesorectal excision; PME, partial mesorectal excision; RCT, randomized controlled study; UK, unknown; NA, not applicable.

^aSignificance shown in both univariate and multivariate analysis.

^bPresented with median (interquartile range).

^cPresented with mean or mean (standard deviation).

Table 2. LARS Score Assessment After AR for No/Minor/Major LARS.

Study	No LARS (%)	Minor LARS (%)	Major LARS (%)	Total
Bregendahl, Denmark, 2013	334 (36)	221 (23)	383 (41)	938
Emmertsen, Denmark, 2013	53 (29)	46 (25)	84 (46)	183
Bondeven, Denmark, 2015	78 (62) ^a		47 (38)	125
Qin, China, 2017	41 (29)	38 (27)	63 (44)	142
Sturiale, Italy, 2017	49 (53)	25 (27)	19 (20)	93
Croese, Australia, 2018	41 (64) ^a		23 (36)	64
Sun, China, 2019	27 (12)	74 (34)	119 (54)	220
Bohlok, Belgium, 2019	12 (28) ^a		31 (72)	43
D'Alba, Italy, 2020	4 (15) ^a		22 (85)	26
Sandberg, Sweden, 2020	161 (42) ^a		225 (58)	386
Theodoropoulos, Greece, 2020	20 (26)	12 (15)	46 (59)	78
Dulskas, Lithuania, 2021	37 (73) ^a		14 (27)	51
Total	1273 (54)^a		1076 (46)	2349

^aSince data of no LARS and minor LARS were not provided, respectively, only the combined amount of the 2 could be presented.

study reported by Sturiale et al, with a median follow-up of 164.4 days (range 130.8-216 days). Preoperative radiotherapy was administrated to 808 (34%) patients, and the treatment duration was mainly long course. Ten studies (except for those performed by Bohlok et al and Dulskas et al) reported that preoperative radiotherapy was associated with significant long-course bowel dysfunction in patients who underwent AR for treatment of rectal cancer. It is worth noting that after adjustment for confounders such as ileostomy and tumor height, 6 studies^{15,16,18-21} showed the significance of adverse effects of preoperative radiation, while the other 4^{3,22,23,25} did not further confirmed that in multivariate analyses.

Primary outcomes. The meta-analysis of LARS included 1654 patients from 6 studies,^{16,18-21,23} and 68% of them (n = 1130) reported major or minor LARS (Table 2). LARS was significantly more common in the preoperative radiotherapy group with an OR of 3.59 without heterogeneity between the included studies (95% CI 2.68-4.81, $P < .00001$, $I^2 = 0\%$, $\chi^2 = 0.80$) (Figure 2A).

With regard to major LARS, 46% of patients (n = 1076) reported this condition (Table 2). The pooled analysis included 2349 patients from the whole 12 studies. Major LARS was significantly more common in the preoperative radiotherapy group, with an OR of 3.28 and moderate levels of heterogeneity

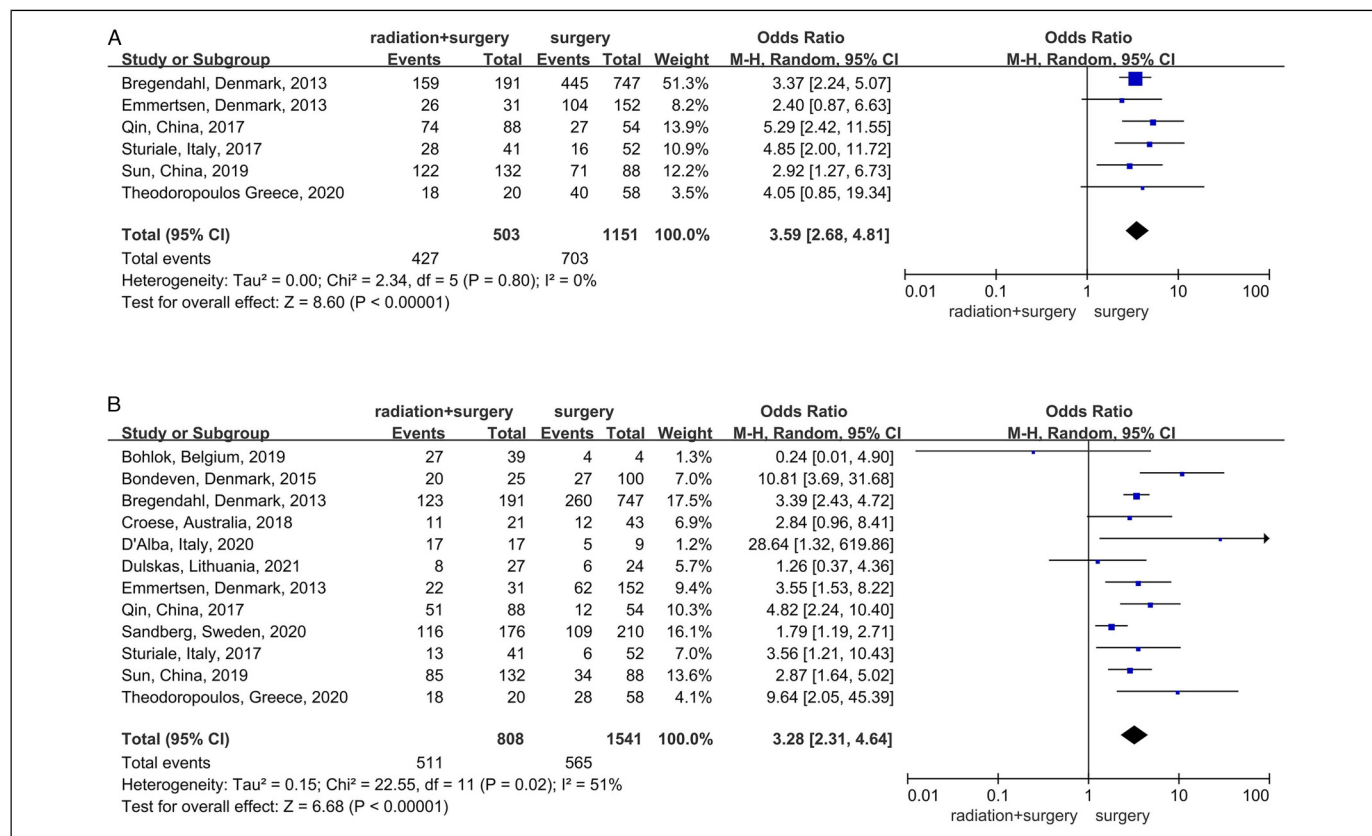


Figure 2. Primary outcomes: (A) LARS, (B) Major LARS.

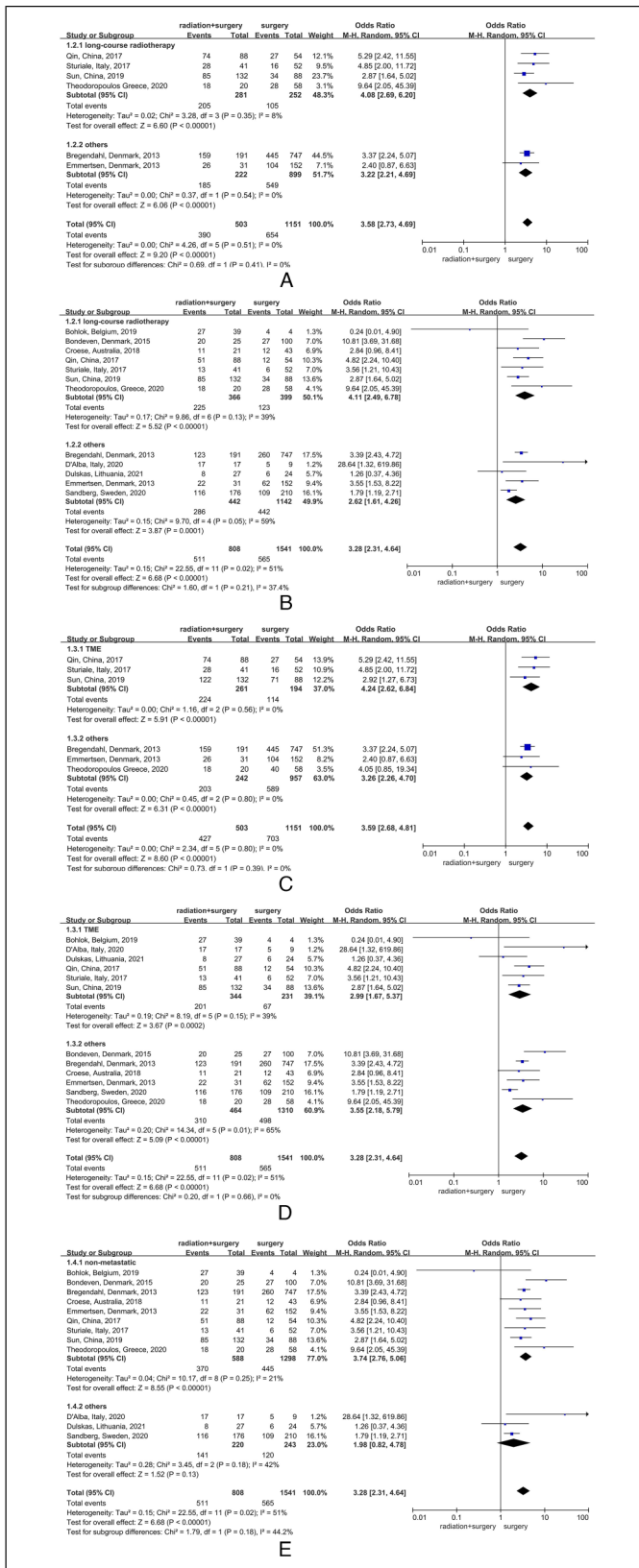


Figure 3. Secondary outcomes: (A) LARS for long-course radiotherapy, (B) Major LARS for long-course radiotherapy, (C) LARS for TME, (D) Major LARS for TME, (E) Major LARS for nonmetastatic rectal cancer.

between the included studies (95% CI 2.31-4.64, $P < .00001$, $I^2 = 51\%$, $\chi^2 = 0.02$) (Figure 2B).

Secondary outcomes. We performed subgroup analyses of long-course radiation, TME, and non-metastatic tumors. LARS and major LARS were selected as outcome variables. Major LARS alone was analyzed in the TME subgroup, and data on LARS were unavailable. Eventually, the results of subgroup analysis of secondary outcomes concurred with those observed for the primary outcomes (Figure 3).

Discussion

This systematic review and meta-analysis determined the effect of neoadjuvant radiotherapy on long-term bowel function in patients who underwent AR for rectal cancer. Considering the low efficacy, clinicians should cautiously evaluate the indications of neoadjuvant therapy to ensure favorable oncological outcomes and inform patients regarding the risk of functional outcomes. A variety of studies across Asia, Europe, America, and Oceania were included in our research, and these may be representative of the worldwide population to a certain extent. Although a few studies did not contain specific data, the included literatures were qualified for the assessment by NOS, and their baseline characteristics were also basically comparable.

The follow-up duration after rectal surgery or ileostomy closure was at least 12 months in all studies included in our research, except for the study reported by Sturiale et al.²⁰ Previous studies^{26,27} have reported that bowel function may gradually recover over time after rectal cancer surgery, and it usually stabilizes approximately one year postoperatively. However, dynamic changes in bowel function cannot be ignored. A prospective multicenter study²⁵ revealed that the major LARS was reported in 63% of participants over one year, which reduced to 56% during the following year. Although symptoms are likely to improve over time, major LARS is a common and chronic complication, particularly in elderly patients, which is confirmed by several studies^{25,28,29} with long-term longitudinal follow-up. Since colorectal cancer is increasingly being diagnosed in young patients in recent times,³⁰⁻³² postsurgical bowel dysfunction is likely to continuously reduce QOL of patients and their families.

The Wexner score³³ was the first incontinence scoring system to include pad use, lifestyle changes, frequency of incontinence, and consistency for the evaluation of patients. This scale is used to quantify the degree of fecal incontinence in patients who undergo AR to treat rectal cancer. In 2012, Emmertsen et al³⁴ developed the LARS score, a valid and reliable scoring system, which is correlated with QOL and facilitates clinical evaluation of the severity of LARS. Since part of the assessment is based on subjective feelings, the score could be influenced by individual personality and emotion. Currently, the LARS score widely used for evaluation of bowel dysfunction owing to its high sensitivity and specificity in identification of QOL impairment. In view of the popularity

and representativeness of the LARS score, we used this scoring system as the targeted assessment scale in this study. Notably, there were also other scales^{35–37} used to evaluate QOL, including bowel, urinary, and sexual function, which is worthy of reference. We originally planned to include urinary and sexual function as well as quality of life as secondary outcomes. However, since they were hard to synthesize from various studies, we decided to drop the metrics during the analysis.

We performed a subgroup analysis of treatment with TME because the risk of anastomotic leakage and bowel dysfunction is higher in cases of TME than in cases of PME,^{18,38} although TME is currently the standard surgical procedure for D3 radical resection in patients with rectal cancer. Croese et al¹⁷ also observed that compared with long-course nCRT, short-course radiotherapy tended to be associated with major LARS (OR 2.4, 95% CI 0.37–15.3, $P = .35$), although the difference was statistically nonsignificant. However, there were also early prospective RCTs reporting that short-course radiotherapy could significantly increase the risk of major LARS.^{28,39}

The primary outcome of LARS showed low heterogeneity ($I^2 = 0\%$), whereas that of major LARS showed moderate heterogeneity ($I^2 = 51\%$) in this study. Cases with stage IV disease tend to result in heterogeneity; therefore, we extracted cases of nonmetastatic tumors and reanalyzed our data. The results showed a reduction of heterogeneity ($I^2 = 21\%$) when we excluded a study that discussed metastatic lesions and another without applicable data on tumor stage.

Concerning the negative effects that radiotherapy may cause like rising risk of anastomotic leakage and bowel dysfunction, it is important to precisely identify the radiotherapeutic indications for patients with rectal cancer. Careful decision-making regarding such patients is essential in perioperative period. This may help a significant proportion of patients avoid experiencing adverse consequences of overtreatment. Researchers have developed many methods as potential predictors of the response of rectal cancer to radiotherapy, based on radiomics-based prediction models,⁴⁰ as well as tissue- and blood-based molecular biomarkers,⁴¹ among other such methods.^{42,43} Given the circumstance, Battersby et al⁴⁴ developed the first nomogram and online tool to predict bowel dysfunction severity before AR and introduced this as the preoperative LARS score, which is called POLARS. Based on predictive factors including age, tumor height, TME or PME, stoma, and preoperative radiotherapy, the risk of bowel dysfunction can be quantitatively determined, helping surgeons accordingly select the optimal treatment strategy and also identify patients who may require additional postoperative support.

Besides, the effects of neoadjuvant chemotherapy alone on perioperative safety,⁴⁵ tumor prognosis,⁴⁶ and bowel function^{47,48} have been studied and discussed in recent years, and its feasibility was confirmed. Some scholars even tried to explore the efficacy of selective radiotherapy based on neoadjuvant chemotherapy.⁴⁹ All patients with LARC received mFOLFOXIRI for 4 to 6 cycles and then assessed clinical response. Responders would have immediate TME while others would receive radiotherapy before surgery. The percentage of tumor downstaging, pathologic complete response rate, 3-year disease-free survival rate,

and safety were determined, and all were found to be comparable. Nevertheless, these findings should be referenced on the occasions when neoadjuvant therapy options were discussed, although nCRT or short-course radiotherapy is still standard treatments for LARC.

In addition, the watch-and-wait approach for patients with clinical complete response after neoadjuvant treatment is increasingly being attempted in clinical practice.^{50,51} Better bowel and urinary functions were found in the group of total neoadjuvant treatment. Moreover, a meta-analysis including 34 studies with 867 patients reported that no difference of oncological outcome was observed, although the study was limited by the quality and heterogeneity of the included studies. In view of the advantages of this strategy, it is likely to be a research hotspot in the future.

Followings are the limitations of this study: (a) No RCT was included, which led to a risk of bias, although we did include 2 secondary RCTs with post hoc analyses. Guidelines have standardized the indications for nCRT in recent years; therefore, it was difficult to ensure randomization, double-blinding, and group concealment in the study design. (b) Bowel dysfunction is more often observed in patients with distal rectal cancer. It would be more meaningful to analyze these cases independently; however, no study presently reported in the literature provides information on low rectal cancer, which may have led to bias in the analyses. (c) The 2 outcomes were heterogeneous in this meta-analysis. Sensitivity analyses showed that the study by Dulskas et al²⁴ led to heterogeneity. We observed this finding even after the aforementioned study was removed from the analysis. Patients receiving nCRT tend to undergo lower anastomosis and ileostomy with different selections for mesorectal excision varying across countries and geographical areas. In addition, the outcome of the LARS score was cross-sectional assessment, and therefore, there were undeniable differences in follow-up time across studies and also each patient. All of the above limitations have contributed to the heterogeneity among the included studies.

In summary, post-AR bowel dysfunction is attributable to several factors. Among the 9 articles in which preoperative radiotherapy was shown to result in bowel dysfunction, 3 articles^{17,22,23} did not report multivariate analysis of confounding factors, which therefore cannot rule out the effects of anastomosis methods, tumor height, or other factors on the results. Further RCTs are warranted, and higher levels of evidence are essential to confirm the association between preoperative radiotherapy and bowel dysfunction in this patient population.

Conclusion

Based on the available evidence, it is reasonable to conclude that preoperative radiotherapy negatively affects long-term bowel function in patients who undergo AR for rectal cancer.

Authors' Note

The systematic review was not subject to ethical review. The study was registered before analysis at the International Prospective Register of Systematic Reviews (CRD42021257988).


Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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