Systematic review and/or Meta-analysis

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Oncologic outcomes of intersphincteric resection versus abdominoperineal resection for lower rectal cancer: a systematic review and meta-analysis

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Background: The efficacy of intersphincteric resection (ISR) surgery for patients with lower rectal cancer remains unclear compared to abdominoperineal resection (APR). The aim of this study is to compare the oncologic outcomes for lower rectal cancer patients after ISR and APR through a systematic review and meta-analysis.

Materials and Methods: A systematic electronic search of the Cochrane Library, PubMed, EMBASE, and MEDLINE was performed through January 12, 2022. The primary outcomes included 5-year disease-free survival (5y-DFS) and 5-year overall survival. Secondary outcomes included circumferential resection margin involvement, local recurrence, perioperative outcomes, and other long-term outcomes. The pooled odds ratios, mean difference, or hazard ratios (HRs) of each outcome measurement and their 95% CIs were calculated.

Results: A total of 20 nonrandomized controlled studies were included in the qualitative analysis, with 1217 patients who underwent ISR and 1135 patients who underwent APR. There was no significant difference in 5y-DFS (HR: 0.84, 95% CI: 0.55–1.29; $P = 0.43$) and 5-year overall survival (HR: 0.93, 95% CI: 0.60–1.46; $P = 0.76$) between the two groups. Using the results of five studies that reported matched T stage and tumor distance, we performed another pooled analysis. Compared to APR, the ISR group had equal 5y-DFS (HR: 0.76, 95% CI: 0.45–1.30; $P = 0.31$) and 5y-LRFS (local recurrence-free survival) (HR: 0.72, 95% CI: 0.29–1.78; $P = 0.48$). Meanwhile, ISR had equivalent local control as well as perioperative outcomes while significantly reducing the operative time (mean difference: − 24.89, 95% CI: − 45.21 to − 4.57; $P = 0.02$) compared to APR.

Conclusions: Our results show that the long-term survival and safety of patients is not affected by ISR surgery, although this result needs to be carefully considered and requires further study due to the risk of bias and limited data.

Keywords: abdominoperineal resection, hazard ratio, intersphincteric resection, lower rectal cancer, oncologic outcome

Rectal cancer accounts for ~30% of colorectal cancer and constitutes a severe global public health burden[1]. Abdominoperineal resection (APR) has long been considered a standard surgical procedure for lower rectal cancer (LRC) located within 5 cm of the anal verge[2] and markedly improves patient survival. As the APR procedure requires permanent colostomy, concerns for the postoperative quality of life (QoL)[3] in combination with technical advances in tumor resection and device-assisted anastomoses have allowed for the development of sphincter-preserving procedures for LRC[4]. With the widespread adoption of neoadjuvant therapy and a total mesorectal excision surgical approach[5], the management of LRC has shifted significantly. The rise of intersphincteric resection (ISR), as established by

HIGHLIGHTS

- To our knowledge, this is the first meta-analysis comparing the oncological outcomes of intersphincteric resection (ISR) and abdominoperineal resection.
- ISR can be recommended for lower rectal cancer as a curative procedure without a permanent colostomy for patients with adequate sphincter function, no risk of positive circumferential resection margin, and guaranteed negative distal margins.
- ISR has comparable long-term survival, local control, and safety compared to abdominoperineal resection and therefore is an alternative surgery for selected patients with lower rectal cancer.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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International Journal of Surgery (2024) 110:2338–2348

Received 12 June 2022; Accepted 20 November 2022

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery.

Published online 17 March 2023

http://dx.doi.org/10.1097/JS9.0000000000000205

Schiessel *et al*.[6], provided an alternative method for radical tumor resection combined with sphincter preservation for LRC patients.

With the gradual application of ISR surgery in clinical practice, various studies have emerged reporting single-institutional or multi-institutional experience with ISR, which has seemingly been proposed to achieve sphincter preservation without compromising local control or survival for tumors at or below 5 cm from the anal verge[7–10]. However, some studies have given different results as to whether ISR can be an alternative or even a replacement for APR[11,12]. Except for the concern of oncological outcomes, the majority of patients who underwent ISR suffered bowel dysfunction, especially in defecation, which may be worse than permanent stomas. Given the debate between APR and ISR as appropriate surgical management for LRC, this systematic review seeks to compare the oncologic outcomes following these two approaches.

Materials and Methods

This review was completed in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)[13], Supplemental Digital Content 1, http://links.lww.com/JS9/A19, Supplemental Digital Content 2, http://links.lww.com/JS9/A20 and *AMSTAR* (Assessing the methodological quality of systematic reviews)[14], Supplemental Digital Content 3, http://links.lww.com/JS9/A21 guidelines and has been registered with Prospero under the registration number CRD42022301556.

Data sources and search strategies

To compare APR with ISR in the management of LRC, a systematic electronic literature search was performed in the Cochrane Library, PubMed, EMBASE, and MEDLINE databases to identify relevant studies published prior to January 12, 2022. The search was confined to studies published in English. The following search terms were used with Boolean operators AND, OR, and NOT: "*rectal*," "*cancer*" or "*carcinoma*" or "*malignancy*," "*abdominoperineal resection*" or "*abdominoperineal excision*," "*intersphincteric resection*," "*sphincter-preserving*" or "*sphincter-saving*" or "*anus-sparing*." See Supplementary Material 1, Supplemental Digital Content 4, http://links.lww.com/JS9/A22 for specific search strategies on each platform. Related Medical Subject Headings (MeSH) were also searched. All references of included studies were reviewed to broaden the search for potentially eligible studies.

Study selection and eligibility criteria

The inclusion criteria for this review were patients with confirmed LRC by proctoscopy and histopathological findings; evaluation of both ISR and APR (open, laparoscopic, or robotic); comparative studies; inclusion of at least one or more outcomes of interest; reporting hazard ratios (HRs) or Kaplan–Meier curves with 95% CIs; and full-text accessibility.

The following publications were excluded: studies with fewer than 10 patients; reviews, case reports, letters, editorials, and noncontrolled trials; and non-English studies.

Definition of main outcome

The primary outcomes included 5-year disease-free survival (5y-DFS) and 5-year overall survival (5y-OS). Secondary outcomes included circumferential resection margin (CRM) involvement, local recurrence (LR), operative time, number of lymph nodes harvested, QoL, postoperative morbidity and mortality, 5-year local recurrence-free survival (5y-LRFS), and 5-year recurrence-free survival (5y-RFS).

In this study, DFS was defined as the duration from the date of surgery to confirmed recurrence or death from any cause, and OS was defined as the duration from the date of surgery to the date of proven death from any cause.

Trial identification and data extraction

Two reviewers (Q.D. and W.M.Y.) screened the titles and abstracts of the search results independently and then assessed the remaining full-text articles for eligibility. Potentially relevant articles were reviewed in full. The full-text evaluation was also conducted for review articles to identify more possible studies. For articles that, although data from the same database were published differently as the number of included individuals increased and the follow-up time increased, only the most recent or most complete version was considered. Both reviewers then assessed the methodological quality of eligible articles independently and extracted data for pooled analyses. We extracted relevant general characteristic data of selected articles, including the year of publication, first author, study type, number of included patients, number of T3 and T4 substage patients, distance from the anal verge, number of cases with neoadjuvant therapy, median follow-up period, and all outcomes of interest. We will e-mail the original author for those missing data. If reviewers agreed that a study did not meet the eligibility criteria, the study was excluded. Discrepancies between the two reviewers were resolved via a discussion by a third author (L.Y.).

Assessment of methodological quality

To assess the methodological quality of included nonrandomized controlled studies, we used the Newcastle–Ottawa scale (NOS) for cohort studies utilizing a star system to score studies from 0 (worst) to 9 (best) stars. Each included cohort study was evaluated on three dimensions: case selection (0–4 stars), comparability (0–2 stars), and outcome (0–3 stars). If the total score was less than five, the study was considered to be of low quality and was not included in this study. If it was greater than or equal to five points, then the subsequent analysis was carried out.

Statistical analysis

Review Manager v5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analyses. The odds ratio (OR) was chosen as an effect measure to compare dichotomous variables. The mean difference (MD) was used for the analysis of continuous variables, and the HR was selected for survival analyses. If the mean and standard deviation were not available from the article, then the method of McGrath *et al*.[15] was used to estimate the median and range. The log hazard ratio (lnHR) and its relevant SEs were calculated by approximating the data of the Kaplan–Meier survival curves included in original articles utilizing Engauge Digitizer v11.1 (Free Software Foundation Inc.) and processing the data via the

Calculations Spreadsheet in Microsoft Excel described by Tierney and colleagues[16,17].

A pooled HR estimate less than 1 demonstrated a better prognosis in the ISR group than in the APR group. A P value lower than 0.05 was defined as statistically significant, and 95% CIs were provided for ORs, MDs or HRs. Statistical heterogeneity between studies was evaluated using the χ^2-test and quantified with Cochrane's inconsistency (I^2)-statistic[18]. We set 50% as a cutoff value, such that I^2 greater than 50% was considered substantial heterogeneity. If the presence of substantial heterogeneity was confirmed, we set up a sensitivity analysis to explore possible causes for the heterogeneity. The possibility of publication bias was estimated primarily by visual analysis of a funnel plot if greater than or equal to 10 studies are available.

Results

Study characteristics

A total of 1394 hits were available through systematic searches of PubMed, Embase, MEDLINE, and the Cochrane Library. After removing duplicates, a total of 820 articles were screened for preliminary titles and abstracts, and then a total of 69 articles were evaluated for eligibility in full text. Among these, 49 articles were excluded because 20 of them were conference abstracts, one was review[19], and one was non-English article[20]. In addition to these, 13 articles[9,21–30] had no control group, seven articles[31–37] had unavailable data, seven articles[7,38–43] were not relevant to our study topic, and one article[44] had data that overlapped with a previous articles. Any disagreements regarding article exclusion were resolved by adding a third reviewer's opinion.

Twenty articles[11,12,43,45–61] were included for qualitative analysis, with a total of 1217 patients in the ISR group and 1135 patients in the APR group. Among the 20 studies, eight were from Europe, 11 were from Asia, and one was from the United States. All 20 studies were nonrandomized controlled studies, two of which were prospective studies. The remaining 18 were retrospective studies, three of which used propensity score matching analysis and two of which had matched baseline data. When using the NOS for literature quality assessment, all articles scored 5 or more points, of which six were scored 8, five were scored 7, eight were scored 6, and one was scored 5.

The sample sizes included in the studies ranged from 27 to 350, and the median follow-up time ranged from 26 to 80.4 months. Twenty articles published between 1992 and 2021 are characterized in Table 1. The mean age of patients who underwent ISR was 59.56 years (range: 26–86 years), while the mean age of patients who underwent APR was 62.47 years (range: 21–90 years). The percentages of males in the two groups were 68.14 and 65.24%, respectively. In ISR, the range of tumor distance from the anal verge was 1–5 cm, and in APR, the range was 0–6 cm. There was no difference in the number of people receiving preoperative neoadjuvant therapy between the two groups (OR: 1.10, 95% CI: 0.75–1.62; $P = 0.62$).

For surgery of LRC, tumor T stage and distance from the anal verge are very important baseline data. However, of the 20 included studies, only five studies had consistent T staging and distance between the two groups of patients, three[45,51,53] of which matched using propensity score matching, and the other two[46,54] had no significant difference between these two characteristics. Therefore, in addition to the pool analysis of all available studies, we selected these five studies for quantitative analysis again. The PRISMA flow chart was shown in Figure 1 [62].

Outcomes

5y-DFS and 5y-OS

For all available studies, five studies[46,48,50,53,61] described 5y-DFS, with a median 5y-DFS of 72% (range: 69–76.30%) after ISR and 63% (range: 42–64%) after APR, with a clear difference between the two groups. The 5y-DFS of the two groups did not differ significantly based on the pooled data from these five studies (HR: 0.84, 95% CI: 0.55–1.29; $P = 0.43$) (Fig. 2A).

When we perform pooled analysis again for those five matched studies[45,46,51,53,54], two studies[46,53] were included, and the results showed no significant difference (HR: 0.76, 95% CI: 0.45–1.30; $P = 0.31$). Fixed-effects models were used because no significant heterogeneity was seen ($I^2 = 17\%$) (Fig. 2B).

Seven of the 20 studies[11,46,48–50,59,61] reported 5y-OS, with a median 5y-OS of 80% (range: 63–86%) after ISR and 57% (range: 46–70%) after APR, with a notable gap between the two groups. However, the pooled result showed no significant difference in 5y-OS between the two groups (HR: 0.93, 95% CI: 0.60–1.46; $P = 0.76$). Bias in selection may be responsible for this. Since no heterogeneity ($I^2 = 0$) was observed, the fixed-effects model was selected (Fig. 3).

Among five matched studies[45,46,51,53,54] based on stage and distance, forest plots were not drawn given that only one study[46] documented OS.

CRM involvement

For all available studies, 12 studies[11,12,43,45,47,48,50–54,58] described CRM involvement. The median CRM positivity rate was 6.74% (range: 0–13.51%) after ISR and 13.55% (range: 0–26.09%) after APR.

When pooling the five screened studies[45,46,51,53,54] for analysis, we found no significant difference between the ISR group and the APR group (OR: 0.76, 95% CI: 0.36–1.58; $P = 0.46$). Because there was no heterogeneity between studies, a fixed-effects model was chosen ($I^2 = 0\%$) (Fig. 4).

LR

A total of 15 articles[11,12,45–47,49,51–54,56,57,59–61] reported postoperative LR rates, with a median LR of 7.79% (range: 0–23.33%) after ISR and 15.71% (range: 0–21.15%) after APR.

The pooled analysis of five matched studies[45,46,51,53,54] showed that the LR rate after ISR was not significantly different from APR (OR: 0.63, 95% CI: 0.39–1.03; $P = 0.07$). Because there was no apparent heterogeneity, we chose a fixed-effects model ($I^2 = 19\%$) (Fig. 5).

Postoperative morbidity and mortality

A total of 11 studies[11,12,43,45–47,53,54,56,57,61] documented overall postoperative morbidity. Our review identified a median postoperative morbidity of 26.92% (range: 15.73–48.48%; 206/712) for ISR and 32.69% (range: 25.71–68.00%; 305/790) for APR.

Four of the five matched studies[45,46,53,54] reported postoperative morbidity, and pooled results showed no significant

Table 1

General characteristics of the included studies

	Region	Inclusion period	Number of patients (ISR/APR)	Distance from anal verge (cm)	T3 + T4 (ISR/APR)	Neoadjuvant therapy		Study design	Median follow-up (months)	Outcomes	NOS
						ISR	APR				
Akagi (2013)[60]	Japan	2001–2011	124/60	≤ 4 cm	NA	0	0	P	65	②;③	6
Beppu (2016)[52]	Japan	2003–2015	104/15	≤ 5 cm	104/15	104	15	R	69	①;②	6
Braun *et al.*[59]	Germany	1977–1987	63/77	NA	NA	NA	NA	R	80.4a	②;⑤	6
Dumont *et al.*[58]	France	1995–2011	14/22	NA	7/10	10	20	R	NA	①	7
Fukuoka (2019)[43]	Japan	2011–2106	NA	≤ 5 cm	NA	NA	NA	R	NA	①;⑦;⑧	6
Hohenberger (2005)[57]	Germany	1985–2001	65/285	NA	NA	NA	NA	R	70	②;⑦;⑧	6
Kim *et al.*[51]	Korea	2006–2011	40/40	NA	24/30	40	40	R; PSM	45.3	①;②;④;⑨	8
Klose (2016)[50]	Germany	2001–2012	60/83	≤ 5 cm	21/54	44	60	R	58	①;⑤;⑥;⑩	7
Konanz *et al.*[56]	Germany	1999–2009	33/50	< 6 cm	10/26	19	28	R	59	②;⑦	7
Koyama *et al.*[49]	Japan	2000–2007	77/33	< 6 cm	50/24	7	6	R	69	②;④;⑤	8
Kuo *et al.*[48]	China	2002–2009	26/23	2.5–5 cm	NA	23	14	R	55	①;⑤;⑥	6
Miyajima *et al.*[55]	Japan	1994–2006	14/14	NA	NA	NA	NA	R	NA	⑩	5
Molnar (2019)[11]	Romania	2011–2013	37/35	1–4 cm	28/20	NA	NA	P	62	①;②;⑤;⑦;⑩	6
He *et al.*[61]	China	2012–2018	43/31	≤ 5 cm	16/18	0	0	R	26; 39b	②;⑤;⑥;⑦;⑧;⑨;⑩	8
Rubinkiewicz *et al.*[54]	Poland	NA	14/13	≤ 5 cm	6/7	11	13	R	NA	①;②;⑦;⑧;⑩	7
Rullier *et al.*[47]	France	1994–2009	186/83	< 6 cm	167/79	166	70	R	52	①;②;⑦;⑧	6
Saito *et al.*[46]	Japan	1995–2006	132/70	1–5 cm	92/47	48	NA	R	40; 57b	②;④;⑤;⑥;⑦;⑧	8
Shin (2021)[53]	Korea	2008–2014	52/52	< 5 cm	39/43	52	52	R; PSM	50.1; 50.5b	①;②;④;⑥;⑦;⑧;⑨;⑩	8
Tsukamoto *et al.*[45]	Japan	2000–2014	89/89	NA	64/63	0	0	R; PSM	60	①;②;③;⑦;⑧;⑨;⑩	8
Weiser *et al.*[12]	America	1998–2004	44/63	≤ 6 cm	38/60	44	63	R	47	①;②;③;⑦;⑧	7

① Positive circumferential resection margin; ② Local recurrence; ③ Recurrence-free survival; ④ Local recurrence-free survival; ⑤ Over survival; ⑥ Disease-free survival; ⑦ Postoperative morbidity; ⑧ Postoperative mortality; ⑨ Number of lymph nodes retrieved; ⑩ Operative time.

aMean.

bThis study reported the respective median follow-up periods for each study group (ISR and APR) rather than the overall follow-up period for the combined patient sample.

APR, abdominoperineal resection; ISR, intersphincteric resection; NA, not available; NOS, Newcastle–Ottawa scale; P, prospective; PSM, propensity score matching; R, retrospective.

difference between the two groups (OR: 0.75, 95% CI: 0.51–1.12; $P = 0.16$). A fixed-effects model was used given that there was no apparent heterogeneity between these studies ($I^2 = 24\%$) (Fig. 6).

A total of nine of the 20 studies[12,43,45–47,53,54,57,61] described postoperative 30-day mortality, with only three postoperative deaths among the 642 patients who underwent ISR compared with 17 deaths among the 705 patients who underwent APR.

Four of the five selected studies[45,46,53,54] reported postoperative mortality, and since there were no cases of postoperative death in the four studies, forest plots were not applicable.

Lymph nodes harvested

The number of lymph nodes recovered by ISR surgery was reported in five of the 20 studies[45,48,51,53,61], with a median number of lymph nodes of 14.30 (range: 11.70–37.00) and a median of 13.40 (range: 9.70–36.00) after APR.

Three of five matched studies were pooled[45,51,53], and the pooled results showed that the number of lymph nodes harvested by the two surgical methods was not significant (MD: 1.30, 95% CI: – 0.60 to 3.19; $P = 0.18$). The fixed-effects model was chosen because no heterogeneity ($I^2 = 0$) was observed (Fig. 7).

Operative time

A total of seven studies[11,45,50,53–55,61] recorded operative time, with a median duration of 261.80 minutes (range: 156.67–374.15 minutes) for ISR procedures and 302.50 minutes (range: 186.78–319.20 minutes) for APR procedures.

In five selected studies, a total of three studies[45,53,54] were pooled, showing no significant difference in operative time between the two surgical procedures (MD: 4.05, 95% CI: – 54.22 to 62.33; $P = 0.89$) and showed greater heterogeneity, so we used a random effects model ($I^2 = 92\%$) (Fig. 8).

Other survival outcomes

Three[12,45,60] and four[46,49,51,53] studies were calculated for 5y-RFS and 5y-LRFS, respectively. The median 5y-RFS after ISR and APR was 81.70% (range: 69.90–83%) and 67.90% (range: 47–70.20%), respectively, and the median 5y-RFS of the two groups was 87.10% (range: 71.20–93.50%) and 79.90% (range: 52.50–87.90%).

In five selected studies, considering that only one study[45] could be pooled for 5y-RFS, no quantitative analysis was performed. Three studies[46,51,53] were available for pooled analysis of 5y-LRFS, and the results showed no significant difference between the two groups (HR: 0.72, 95% CI: 0.29–1.78; $P = 0.48$) and no heterogeneity between studies ($I^2 = 0$) (Fig. 9).

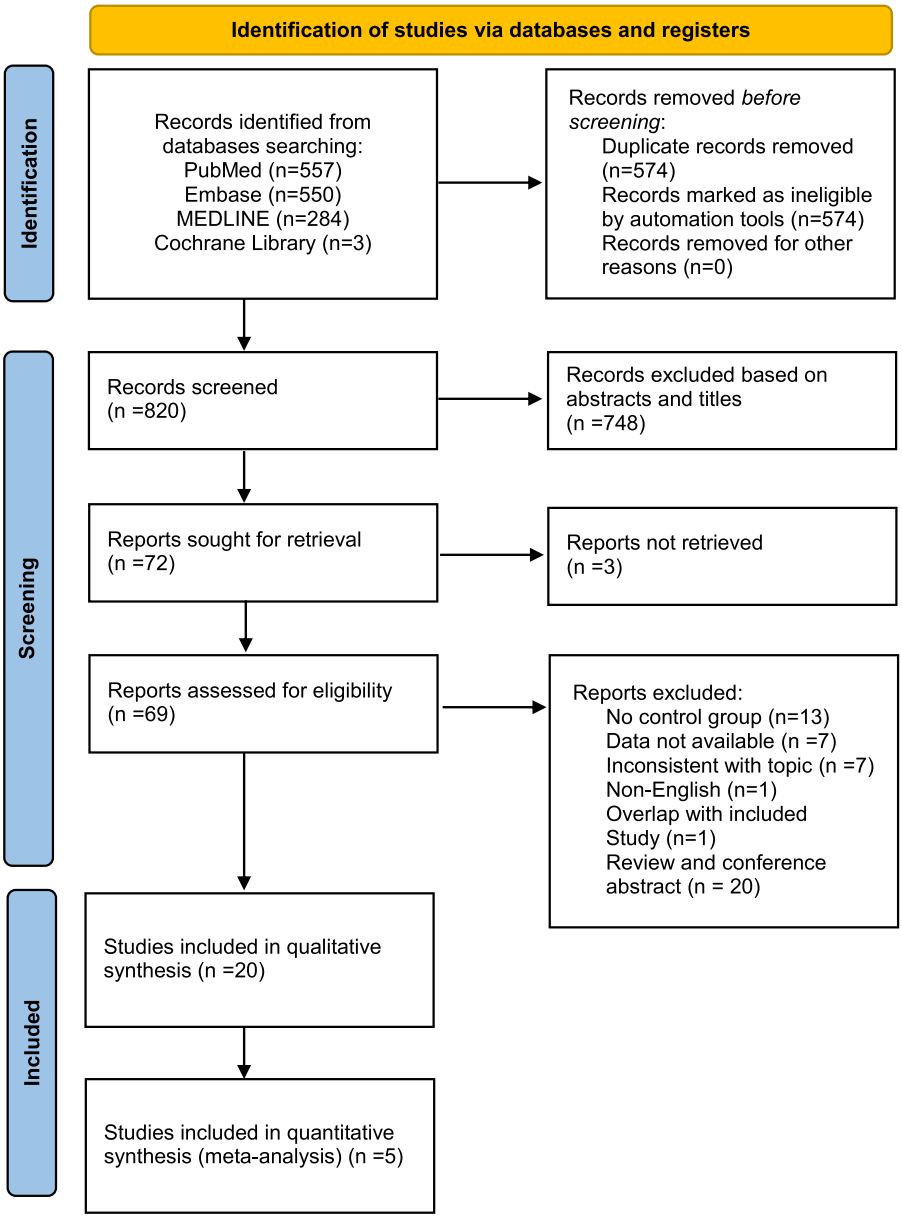

Figure 1. Flow diagram of literature search and study selection.

QoL

Only two of the included studies[56,58] reported on postoperative QoL, so we did not perform a quantitative analysis. Both Konanz *et al.*[56] and Dumont *et al.*[58] showed that patients in the ISR group had significantly worse physical functioning than those in the APR group. Konanz also found a significant reduction in gastrointestinal symptoms in the APR group compared to the ISR group. However, sexual function, especially in men, had more problems in the APR group. The study by Dumont also showed that the APR group had significantly lower defecation problems than the ISR group.

Sensitivity analysis and publication bias

As stated above, there was substantial heterogeneity ($I^2 = 92\%$, $P < 0.00001$) between the studies synthesizing the pooled operative time in the random effects model. After exclusion of each unique study, the deletion of the study Tsukamoto *et al.*[45] was observed to reverse the heterogeneity ($I^2 = 0\%$, $P = 0.84$) (Fig. 10), and the result at this point showed a significantly shorter operative time for ISR than for APR (MD: – 24.89, 95% CI: – 45.21 to – 4.57; $P = 0.02$). Publication bias was not assessed because the insufficient of articles.

Discussion

The rise of ISR provides an alternative technique for LRC patients, while its oncologic outcomes compared to APR remain controversial. In the present meta-analysis, we included 20 articles with moderate to high NOS scores. Among these studies, seven studies[12,46–49,51,59] showed better survival after ISR than

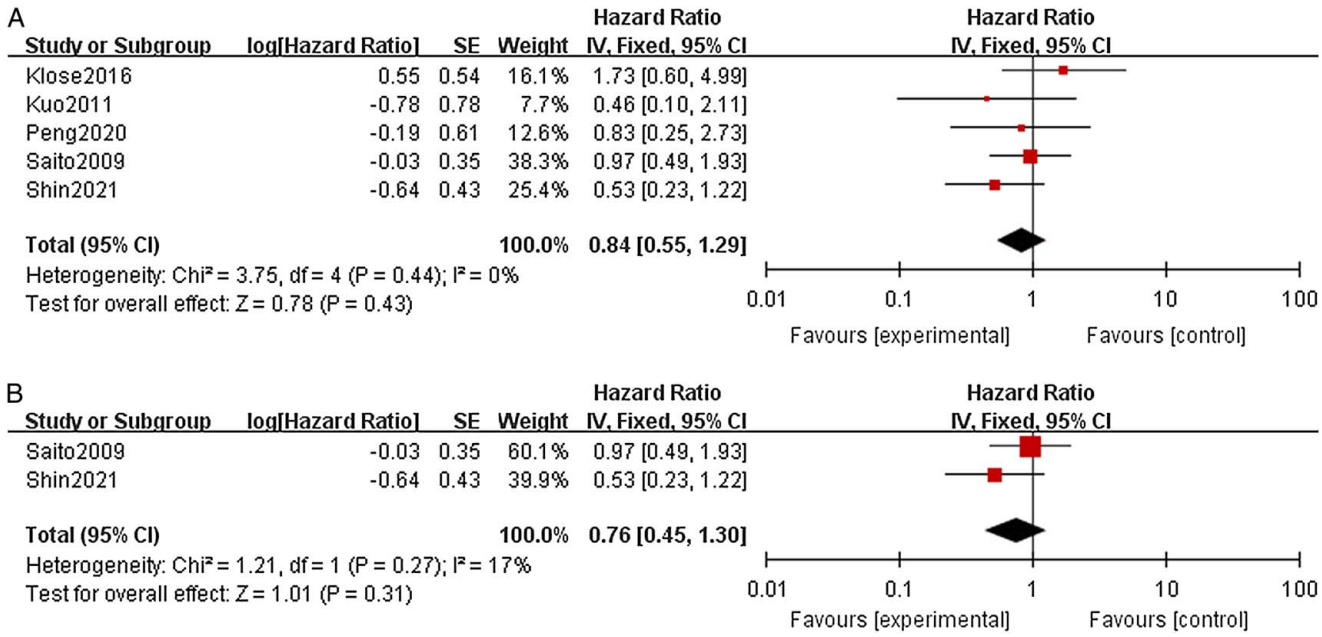

Figure 2. Forest plot of 5-year disease-free survival in all eligible studies (A) and in matched studies (B).

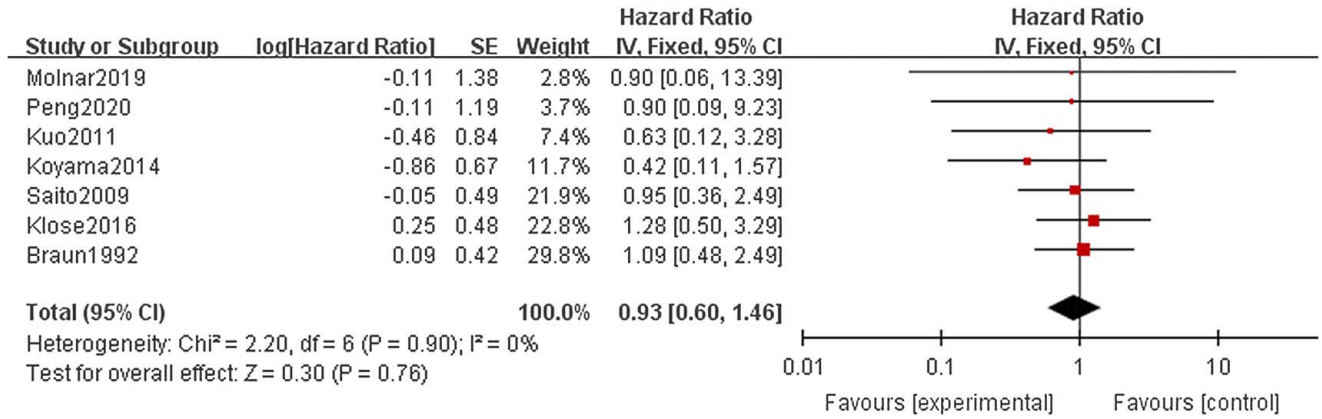

Figure 3. Forest plot of 5-year overall survival.

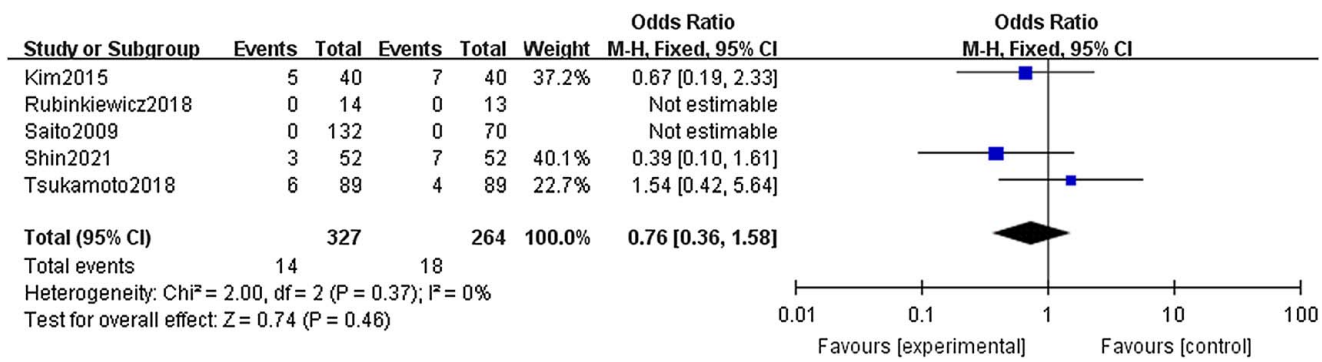

Figure 4. Forest plot of positive circumference resection margin.

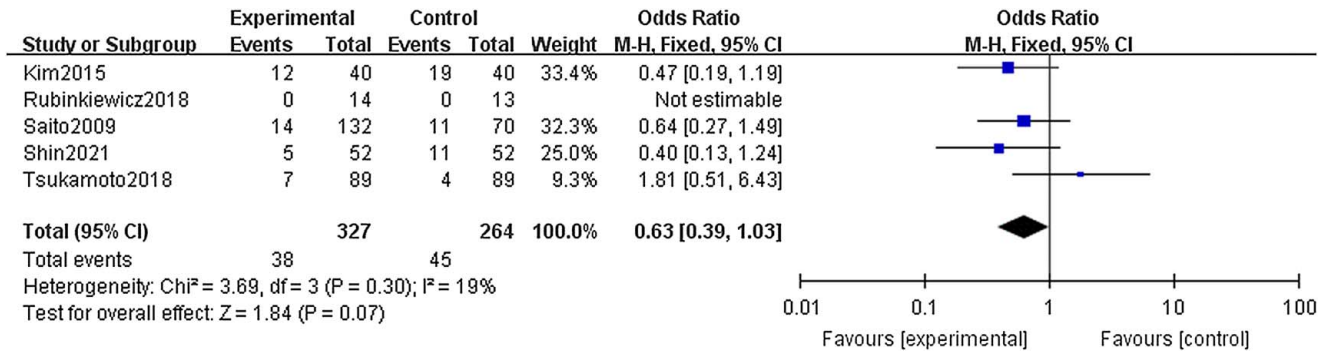

Figure 5. Forest plot of local recurrence.

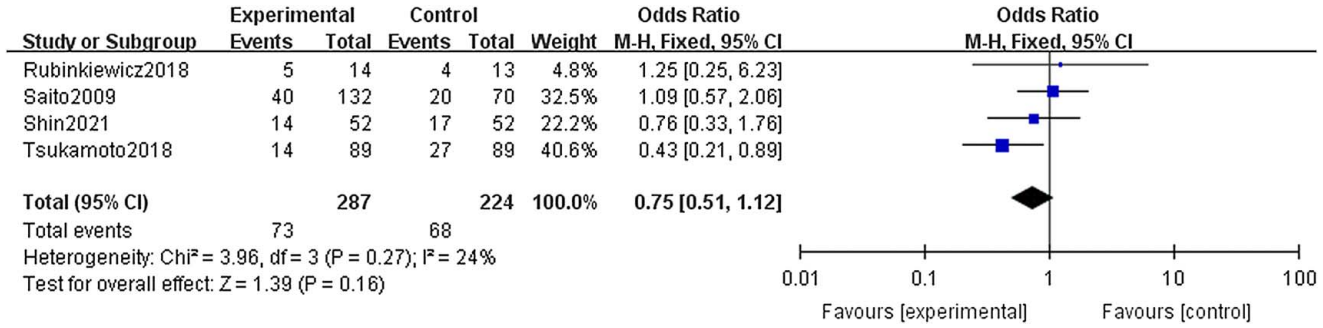

Figure 6. Forest plot of postoperative morbidity.

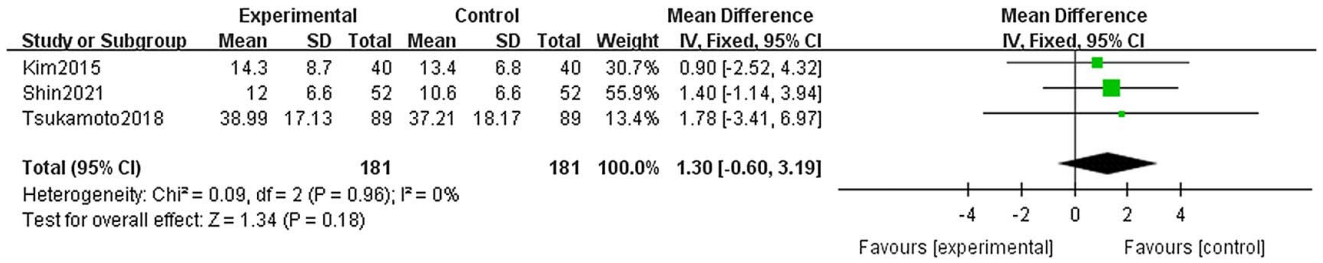

Figure 7. Forest plot of lymph nodes harvested.

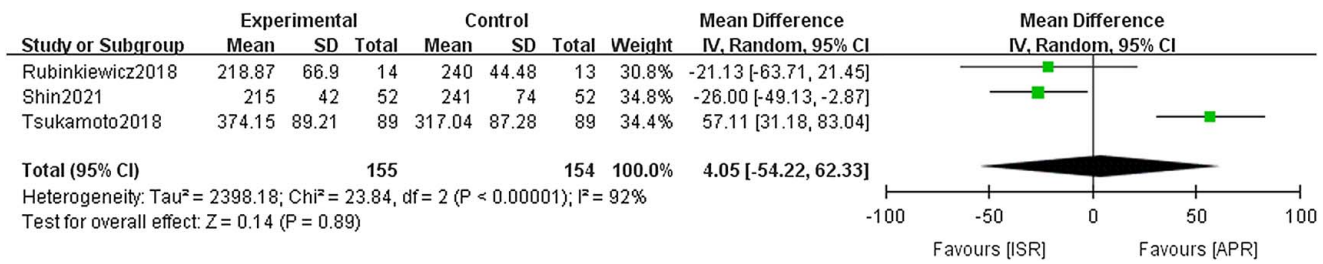

Figure 8. Forest plot of operative time.

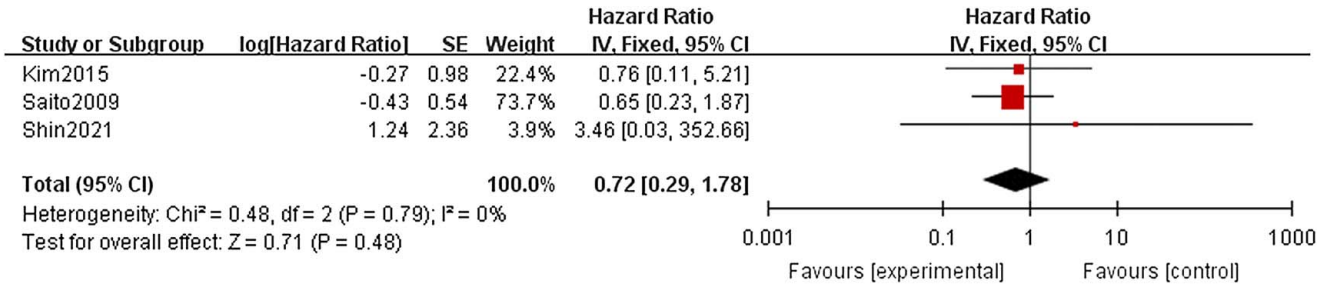

Figure 9. Forest plot of 5-year local recurrence-free survival.

after APR, and six studies[11,12,47,48,51,56] showed better CRM or LR. However, the majority of these studies had significant differences in the T stage and in the distance of the tumor from the anus, which are two important factors affecting the prognosis of LRC patients. Generally, those with tumors that were closer to the anus or those with more advanced tumor stages often tended to receive APR surgery. Therefore, we conducted a meta-analysis after controlling for variables such as tumor T stage and distance from the anus. The pooled analysis showed that ISR had comparable DFS, OS, CRM positive rate, LR, and LRFS compared with APR, while perioperative outcomes were not compromised.

A positive CRM is an independent risk factor for patient survival and tumor recurrence after LRC surgery[63,64]. In the traditional Miles procedure, the excision scope is wide, including the whole levator ani and most of the perianal tissue; thus, the risk of CRM involvement is low. Compared to Miles surgery, the ISR procedure has a relatively limited excision scope, and thus, its safety in CRM clearance is a concern of surgeons. Generally, patients who choose ISR surgery should be those with early local stage or down-staged after neoadjuvant therapy without risk of CRM positive in preoperative evaluation. For patients with a high risk of CRM positivity by ISR, Miles surgery should be considered. Therefore, when comparing the efficacy of the two procedures, they should be compared according to the tumor stages, especially T stage. In addition to tumor stage, the distance of the lower margin of the tumor from the anal verge was also an important factor to be considered. Since the infiltration distance of the tumor into the distal bowel wall is often less than 1 cm, the anus-preserving procedure can be performed if the intraoperative flash-frozen section of the distal margin is free of tumor cells. ISR surgery is divided into four types, including partial ISR, subtotal ISR, total ISR, and ISR with simultaneous resection of the invaded levator ani muscle. Selecting a proper procedure for ISR, it is not difficult to ensure a safe distal margin, which has been demonstrated by available studies. So patients with LRC who are candidates for ISR should be those with good anal sphincter function, no risk of positive CRM, and those who can be assured of negative distal margins. In the present meta-analysis, there was no significant difference in distance from the anus and T stage in two studies[46,57], and three studies[45,51,53] were matched so that the two groups were comparable.

Tumor stage not only affects the choice of surgery but also influences long-term survival. Tumors with early staging are often chosen by patients and surgeons for anus-preserving surgery. In seven studies reporting survival outcomes, the median 5y-OS after ISR was 80%, 23% higher than APR, 5y-DFS was nearly 10% higher than APR, and both 5y-RFS and 5y-LRFS were also higher than APR. However, most of these studies were not stage matched, and the result that ISR was better than APR appeared due to the presence of bias. Therefore, we performed this meta-analysis of five studies that were stage-matched, and the pooled results showed no significant difference between the two groups, demonstrating that long-term survival outcomes were not compromised by preservation of the anus.

Our pooled results showed no significant difference in CRM involvement between the two groups, indicating comparable local control for both procedures. Moreover, the LR between the two groups again validated the result, as the pooled data also showed no difference in LR between the two groups. Based on the above results, we can conclude that ISR does not increase the incidence of CRM involvement and LR compared with APR.

Due to the narrow pelvis and complex anatomy, numerous technical challenges are associated with low rectal resection, including the preservation of the genitourinary and autonomic nervous systems, which are associated with patient prognosis and QoL. Therefore, the technique of the surgeon is also an important factor affecting the prognosis. There is a steep learning curve to successfully perform the ISR operation, which may critically

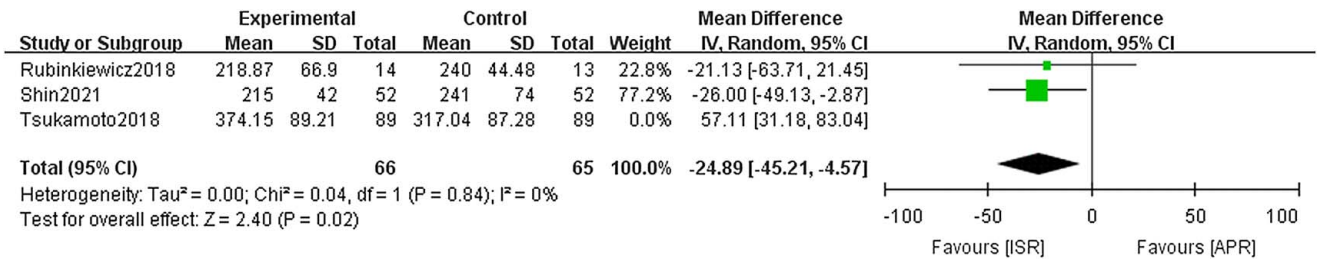

Figure 10. Forest plot for sensitivity analysis of operative time. APR, abdominoperineal resection; ISR, intersphincteric resection.

impact operating time and postoperative complications[65,66]. ISR requires plentiful surgical experience and highly specialized surgical skills, including precise knowledge of rectal anatomy and its anomalies, to avoid injury to critical muscles and autonomic nerves. Due to the delicate nature of the ISR approach, deviations from correct tissue planes may lead to unsafe margins, tumor residue, and increased risk of LR. The studies included in this meta-analysis do not report data regarding the experience of surgeons and the standardization of surgical techniques. Therefore, future analyses comparing ISR and APR and the resulting prognosis for survival outcomes should include rigorous prospective studies or even randomized controlled trials (RCTs), requiring structured training conducted at high-volume surgical centers. The limitations of ISR must be further evaluated to determine the exact indications for this surgery.

Adequate lymph node harvest is essential in the pathological staging and subsequent treatment of patients. Three studies[45,51,53] with an NOS score of eight all reported the number of lymph nodes retrieved after ISR, and all showed that the average number of lymph nodes collected was higher than that of APR. Shin *et al.*[53] reported that the mean number of lymph nodes was 12.00 and 10.60 for each group, respectively, but the difference was not statistically significant ($P = 0.27$), as was the case in the other two studies. Pooling all studies that included operative time revealed no significant difference in operative time between the two surgical procedures, but the heterogeneity was very high at this point, and it was found that the heterogeneity decreased from 92 to 0% after removing the study by Tsukamoto *et al.*[45] and that the operative time was significantly shorter in ISR than in APR at this point. This may be due to the fact that the data for this article were collected from January 2000, before the widespread and mature use of ISR. Regarding postoperative morbidity and mortality, there was no significant difference between the two groups. Whereas, postoperative complications should be considered as an important issue for the balancing of ISR or APR. Even though preventative stomas are usually made in ISR, some patients still have to receive of a permanent stoma due to some unavoidable anastomotic leakage, anastomotic stenosis, and poor bowel function. Some early studies showed a high rate of postoperative complications after ISR, and a study by Köhler *et al.*[7] showed that ~48% of patients developed anastomotic leakage after ISR. However, several recent studies[67–69] have shown postoperative anastomotic leakage and postoperative mortality rates after ISR similar to our results, and the data reported were that the range of anastomotic leakage was 5.1–20% and postoperative mortality was 0–5%. Although there is no risk of anastomotic leakage with APR, there is a high incidence of parastomal hernias (10–50%)[70–72] and perineal hernias (1–26%)[73], as well as complications due to the large trauma of the procedure itself. Therefore, the operator should fully understand the various complications and make a comprehensive preoperative assessment to choose appropriate procedure.

In addition to the requirement for negative resection margins, another factor to consider was the QoL after sphincter preservation. For rectal cancers that were located too low (e.g. tumors involving the dentate line and anal canal), QoL after sphincter preservation was also a concern. There are conflicting reports on the functional outcomes and QoL for patients after ISR compared to APR[49,56,74,75]. Recent studies have challenged the assumption that QoL outcomes are worse in patients with permanent stomas (e.g. APR patients)[74]. In this meta-analysis, we did not compare the long-term functionality and QoL for these two postoperative populations because only two of the included studies mentioned functional outcomes, but our team is conducting a prospective study on the comparison of postoperative QoL between ultimate sphincter-preserving procedures and extralevator abdominoperineal exercise (ELAPE) (ChiCTR2200058417).

This work had several limitations. First, neoadjuvant radiotherapy, another prognostic factor for LRC, was not reported in detail in any of these articles, so we did not consider this factor when conducting our analysis. Second, when pooled analyses of long-term outcomes were performed, the limited number of studies reduced the quality of the results. Finally, our study did not include any RCTs, although all eligible studies were moderate-quality to high-quality cohort studies, as assessed by NOS criteria. Due to ethical issues, direct comparison by an RCT of the two procedures (ISR and APR) is currently virtually impossible. Researchers must keep the balance between patients' desires and bias control. Therefore, there would be more or fewer confounding factors in the existing studies, which can be better solved to some extent by a prospective PSM design in future studies.

Conclusions

This meta-analysis provides a valuable analysis regarding the oncologic outcomes comparing ISR and APR for patients with LRC. Our results demonstrated that ISR would have comparable prognosis and local control, although survival outcomes require careful consideration and further confirmation due to the risk of bias and limited data. Our study is a valuable reference for LRC patients and clinicians to choose surgical methods. ISR can be recommended for LRC as a curative procedure without a permanent colostomy for patients with adequate sphincter function, no risk of positive CRM, and guaranteed negative distal margins. Meanwhile, structured training and advanced surgical techniques for surgeons who perform ISR and intensive surveillance plans after surgery are indispensable. Future large-scale and well-designed clinical trials are warranted to define precise indications and long-term outcomes of ISR to better guide the treatment of LRC.

Ethics approval and consent to participate

Not applicable.

Sources of funding

This work was supported by 1·3·5 project for disciplines of excellence – Clinical Research Incubation Project, West China Hospital, Sichuan University (grant number: 2022HXFH028; 2016105, ZYGD20006).

Author contribution

Q.D., W.Y., Y.W., L.Y., and Z.Z. conceptualized this study and wrote the manuscript. Q.D., J.Z., and S.Q. contributed to data collection and statistical analyses. Q.D., X.L., and L.Y. contributed to results interpretation. All authors reviewed the manuscript, revised it critically for important intellectual content.

Competing interests disclosure

All authors declare that there are no conflicts of interest.

Research registration unique identifying number (UIN)

None.

Guarantor

Lie Yang is the guarantor of this work.

Data statement

All data generated or analyzed and software used during this study are included in this published article.

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