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REVIEW

Meta-analysis of temporary loop ileostomy closure during or after adjuvant chemotherapy following rectal cancer resection: the dilemma remains

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Abstract

Objective To evaluate comparative outcomes of temporary loop ileostomy closure during or after adjuvant chemotherapy following rectal cancer resection.

Methods We systematic searched MEDLINE, EMBASE, CINAHL, CENTRAL, the World Health Organization International Clinical Trials Registry, ClinicalTrials.gov, ISRCTN Register and bibliographic reference lists. Overall perioperative complications, anastomotic leak, surgical site infection, ileus and length of hospital stay were the evaluated outcome parameters. Combined overall effect sizes were calculated using fixed effects or random effects models.

Results We identified 4 studies reporting a total of 436 patients comparing outcomes of temporary loop ileostomy closure during ($n = 185$) or after ($n = 251$) adjuvant chemotherapy following colorectal cancer resection. There was no significant difference in overall perioperative complications (OR 1.39; 95% CI 0.82–2.36, $p = 0.22$), anastomotic leak (OR 2.80; 95% CI 0.47–16.56, $p = 0.26$), surgical site infection (OR 1.97; 95% CI 0.80–4.90, $p = 0.14$), ileus (OR 1.22; 95% CI 0.50–2.96, $p = 0.66$) or length of hospital stay (MD 0.02; 95% CI − 0.85–0.89, $p = 0.97$) between two groups. Between-study heterogeneity was low in all analyses.

Conclusions The meta-analysis of the best, albeit limited, available evidence suggests that temporary loop ileostomy closure during adjuvant chemotherapy following rectal cancer resection may be associated with comparable outcomes to the closure of ileostomy after adjuvant chemotherapy. We encourage future research to concentrate on the completeness of chemotherapy and quality of life which can determine the appropriateness of either approach.

Keywords Loop ileostomy closure · Stoma reversal, adjuvant chemotherapy

Introduction

Rectal cancer is one of the most common cancers worldwide with increasing incidence [1]. A temporary stoma is often used in rectal cancer surgery to protect a distal anastomosis, particularly after low anterior resection (LAR) which is the treatment of choice for rectal cancer of the middle and lower third [2–4]. Patients with a temporary protecting ileostomy (diverting stoma) are at lower risk of anastomotic leak, peritonitis and their associated morbidity and mortality [5, 6].

Loop ileostomies are generally not closed earlier than 2 months after primary surgery. In a large number of patients, this not only is associated with stoma-related morbidities but also would cause discomfort and affect their quality of life [7, 8]. Despite the existence of considerable pressure from the patients to close the protecting stoma as soon as possible, high-level evidence on the optimal timing of stoma closure is lacking. Although early closure of the protecting stoma has been demonstrated to be safe [9–12], it may negatively influence the completeness of chemotherapy due to complications including anastomotic leakage or LAR syndrome [13].

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On the other hand, having an ileostomy during chemotherapy has been shown to increase the risk of high stoma output which subsequently leads to dehydration, electrolyte disturbances and renal failure [14].

Although outcomes of early versus late closure of loop ileostomy following rectal cancer surgery have been investigated before, the outcomes have not been evaluated with respect to adjuvant chemotherapy. Considering the controversies regarding the optimal timing of temporary loop ileostomy closure with respect to time of adjuvant chemotherapy, we aimed to evaluate comparative outcomes of temporary loop ileostomy closure during or after adjuvant chemotherapy following rectal cancer resection.

Methods

Design and study selection

We highlighted our eligibility criteria and methods and evaluated outcomes in a review protocol. Our study was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards [15].

We included all comparative studies evaluating the outcomes of temporary loop ileostomy closure during or after adjuvant chemotherapy following rectal cancer resection. We considered all participants aged 18 years or older and of any gender who underwent a reversal of temporary loop ileostomy.

The intervention of interest was the closure of loop ileostomy during adjuvant chemotherapy. The primary intervention was compared with the closure of loop ileostomy after adjuvant chemotherapy.

Primary outcome measures were defined as overall perioperative (30 days or in hospital) complications (bleeding, surgical site infections (SSIs), anastomotic leak, ileus and incisional hernia). An anastomotic leak was defined as a communication between the intra- and extra-luminal compartments owing to a defect of the integrity of the intestinal wall at the anastomosis between the colon and rectum. We considered anastomotic leaks that were treated either conservatively or surgically. Moreover, we analysed each complication where the complication was reported by more than 1 study. Length of hospital stay was the secondary outcome parameter.

Literature search strategy

Two authors independently searched the following electronic databases: MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL). The literature search was conducted on 24 February 2019. Our search strategy was adapted according to thesaurus headings, search operators and limits in the aforementioned databases (Appendix Table 3). Furthermore, we searched the World Health Organization International Clinical Trials Registry http://apps.who.int/trialsearch/, ClinicalTrials.gov http://clinicaltrials.gov/ and ISRCTN Register http://www.isrctn.com/ to identify ongoing and unpublished studies. Moreover, the bibliographic lists of relevant articles and reviews were screened for further potentially eligible trials. Finally, we hand-searched the leading journals in general surgery and colorectal surgery.

Selection of studies

The title and abstract of identified articles were evaluated by two independent authors. Subsequently, if relevant, the full texts of identified articles were retrieved and evaluated against the eligibility criteria of our study. Those studies that met our eligibility criteria were included. Discrepancies in this process were resolved by discussion between the authors. However, if the disagreement still existed, an independent author was consulted.

Data extraction and management

We created an electronic data extraction spreadsheet according to Cochrane's recommendations for intervention reviews. The data extraction spreadsheet was pilot-tested in randomly selected articles and adjusted accordingly. The following pieces of information were extracted from the included studies by two independent authors:

- Study-related data (first author, publication year, country of origin of the corresponding author, journal in which the study was published, study design and study size)
- Baseline demographic and clinical information of the study populations (stage and distribution of cancer, type of procedure)
- Primary and secondary outcome data

Disagreements during data extraction and management were resolved following consultation with a third independent author.

Assessment of risk of bias

The methodological quality and risk of bias assessment were carried out by two authors using the Newcastle-Ottawa scale (NOS) [16] as all of our included studies were observational studies. The NOS is a star-based scoring system (maximum score 9) which enables review authors to evaluate an observational study in the following aspects: the selection of the study groups, the comparability of the groups and the ascertainment of the outcome of interest. Studies with a score of 9 stars were

deemed to be at low risk of bias, studies with a score of 7 or 8 stars were deemed to be at medium risk of bias and those that scored 6 or less were judged to be at high risk of bias. We resolved discrepancies in the risk of bias assessment by discussion between the assessing authors. Nevertheless, if no agreement could be reached, a third reviewer was involved as an adjudicator.

Summary measures and synthesis

For dichotomous outcome variables (overall complications, anastomotic leak, SSI, paralytic ileus), we calculated the odds ratio (OR) as the summary measures. The OR is the odds of an adverse event in the stoma closure during chemotherapy group compared with the after chemotherapy group. An OR of less than one would favour closure of ileostomy during the chemotherapy. For continuous parameters (length of hospital stay), we calculated the mean difference (MD) between the two groups.

The individual patient was used as the unit of analysis in this study. Information with regard to dropouts, withdrawals and any other missing data were recorded. We planned to contact the authors of the included studies where information about our outcome of interest was not reported. Our final analysis respected the intention-to-treat concept.

One independent review author entered the extracted data into Review Manager 5.3 software for data synthesis [17]. The entered data were subsequently checked by a second independent review author. Random effects or fixed effects modelling were used, as appropriate, for analysis. Only when significant between-study heterogeneity existed, random effects models were applied. This has previously been defined by Higgins et al. [17]. We reported the results of our analysis for each outcome parameter in a forest plot with 95% confidence intervals (CIs).

Heterogeneity among the studies was assessed using the Cochran Q test (χ^2). We quantified inconsistency by calculating I^2 and interpreted it using the following guide: 0 to 25% might not be important; 25 to 75% may represent moderate heterogeneity; 75 to 100% may represent substantial heterogeneity. Moreover, where more than 10 studies were available in analysis of an outcome parameter, funnel plots were planned to be constructed in order to assess their symmetry to visually evaluate publication bias.

We conducted sensitivity analyses to explore potential sources of heterogeneity and assess the robustness of our results. For each outcome parameter, we repeated the primary analysis using random effects or fixed effects models. Moreover, for each of our defined dichotomous variable, we calculated the pooled OR, risk ratio (RR) or risk difference (RD). Finally, we evaluated the effect of each study on the overall effect size and heterogeneity by repeating the analysis following excluding one study at a time.

Results

Our literature search through the aforementioned databases identified 1631 articles. After further evaluation of the identified articles, only 4 articles [18–21] were deemed appropriate for inclusion (Fig. 1). The included studies consisted of 3 retrospective and 1 prospective observational studies reporting a total of 436 patients of whom 183 underwent reversal of temporary loop ileostomy during adjuvant chemotherapy and the remaining 251 had reversal of temporary loop ileostomy after adjuvant chemotherapy.

Table 1 presents the date of publication and country of origin, journal, study design of the included studies and baseline demographic and clinical characteristics of the study populations. The patients in both groups were of comparable age ($p = 0.61$) and gender ($p = 0.59$). There was no significant difference between the study groups in colorectal cancer stage 0 ($p = 0.44$), stage I ($p = 0.53$), stage II ($p = 0.81$), stage III ($p = 0.66$) and stage IV ($p = 0.13$). The mean interval between primary operation and loop ileostomy closure was significantly

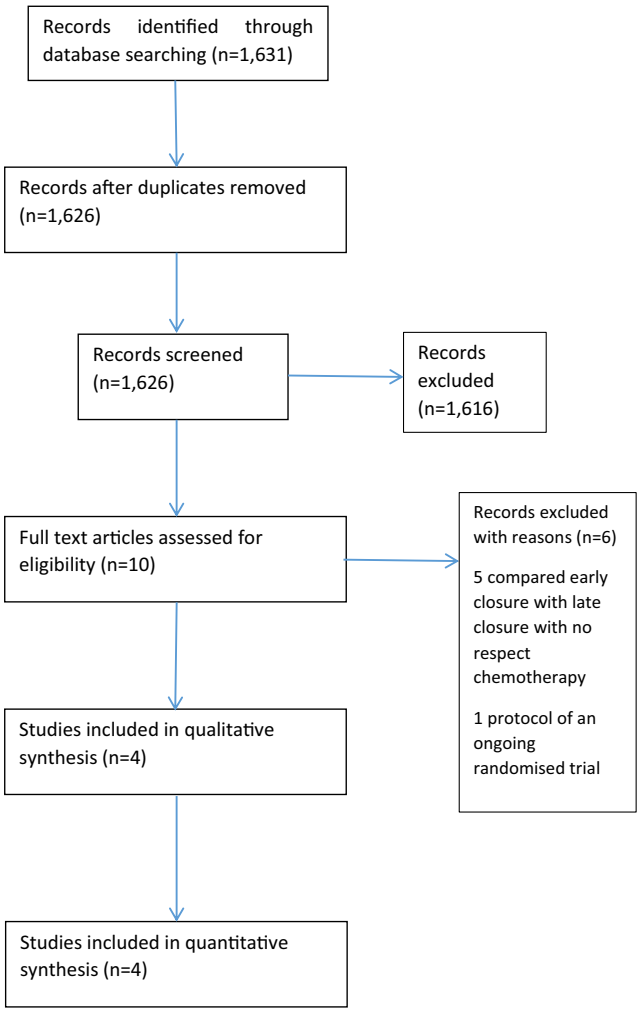


Fig. 1 Study flow diagram

Table 1 Summary characteristics and baseline demographics of included studies

Author	Year	Country	Journal	Design	Reversal during chemo	Reversal after chemo	Mean age	Male:female	Diagnosis	Stage
Zhen [18]	2017	China	Current Problems in Cancer	Prospective observational study	91	70	58.54 ± 11.49 vs 53.99 ± 13.24	64:27 vs 53:17	Rectal cancer	0 or Tis 5 vs 2 I: 21 vs 18 II: 38 vs 32 III: 27 vs 18
Kye [19]	2014	Korea	International Journal of Surgery	Retrospective observational study	55	69	72.7 ± 4.9 vs 74.1 ± 5.5	33:22 vs 47:22	Rectal cancer	0 or Tis 6 (10.9%) vs 12 (17.4%) 1 11 (7.3%) vs 19 (27.5%) 2 18 (32.7%) vs 17 (24.6%) 3 16 (29.1%) vs 19 (27.5%) 4 4 (7.3%) vs 2 (2.9%)
Tulchinsky [20]	2013	Germany	Journal of Surgical Oncology	Retrospective observational study	25	79	61.3 ± 11.3 vs 62.5 ± 11.2	17:8 (68:32) vs 43:36 (54:46)	Rectal cancer	0 4 (16%) vs 18 (23%) I: 12 (48%) vs 13 (16%) II: 4 (16%) vs 22 (28%) III: 5 (20%) vs 26 (33%)
Thalheime [21]	2006	Israel	Disease of Colon and Rectum	Retrospective observational study	14	33	62.7 (50–81) vs 59.4 (25–74)	10:4 vs 25:8	Rectal cancer	I: – – – II: 5 vs 11 III: 5 vs 17 IV: 4 vs 5

Table 2 Methodological quality of the observational studies assessed with the Newcastle-Ottawa scale

Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total score
Zhen [18]	*	*	*	*	*	*	*	*	8
Kye [19]	*	*	*	*	**	*	*	*	9
Tulchinsky [20]	*	*	*	*	**	*	*	*	9
Thalheime [21]	*	*		*	*	*	*	*	7

shorter in patients who had the closure of loop ileostomy during the adjuvant chemotherapy ($p < 0.00001$).

Methodological appraisal

The methodological appraisal of the included 4 studies is presented in Table 2. The risk of bias was judged as low in 2 studies and moderate in the remaining 2.

Data synthesis

Outcomes are summarised in Fig. 2.

Overall perioperative complications Four studies reported overall perioperative complications as an outcome. There were 36 (19.46%) complications in the during chemotherapy group whereas there were 38 (15.14%) complications in after chemotherapy group. The pooled analysis of 436 patients demonstrated that there was no significant difference in overall complications between two groups (OR 1.39; 95% CI 0.82–2.36, $p = 0.22$). Between-study heterogeneity was low (I^2 0%, $p = 0.48$).

Anastomotic leak Three studies (332 patients) reported anastomotic leak as an outcome. The anastomotic leak rates during and after chemotherapy groups were 1.88% and 0.58%, respectively. The pooled analysis showed no significant difference in anastomotic leak rate between the two groups (OR 2.80; 95% CI 0.47–16.56, $p = 0.26$). Heterogeneity among the included studies was low (I^2 0%, $p = 0.97$). Only one study [21] reported the method of anastomosis (ileoileostomy) which was hand-sewn anastomoses.

SSI Three studies reported SSI as an outcome. SSI occurred in 14 (8.75%) and 8 (4.65%) patients during and after chemotherapy groups, respectively. The pooled analysis of 332 patients found no significant difference in SSI rate between the two groups (OR 1.97; 95% CI 0.80–4.90, $p = 0.14$). Low heterogeneity existed among the included studies (I^2 0%, $p = 0.81$).

Ileus Postoperative ileus was reported by 3 studies (332 patients). There was no significant difference in the ileus rate between the during chemotherapy (6.25%) and after chemotherapy groups (6.39%) (OR 1.22; 95% CI 0.50–2.96, $p = 0.66$). There was low between-study heterogeneity (I^2 0%, $p = 0.42$).

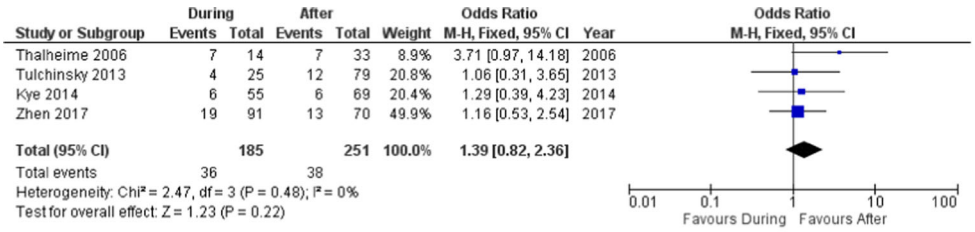
Length of hospital stay Only two studies reported the length of hospital stay as an outcome. The pooled analysis of 265 patients demonstrated that the length of hospital stay was similar in both groups (6.88 days vs 6.91 days, MD 0.02; 95% CI −0.85–0.89, $p = 0.97$). Low heterogeneity among the included studies was detected ($I^2 = 0\%$, $p = 0.35$).

The available data provided by the included studies did not allow us to conduct any analysis on completeness of chemotherapy or quality of life.

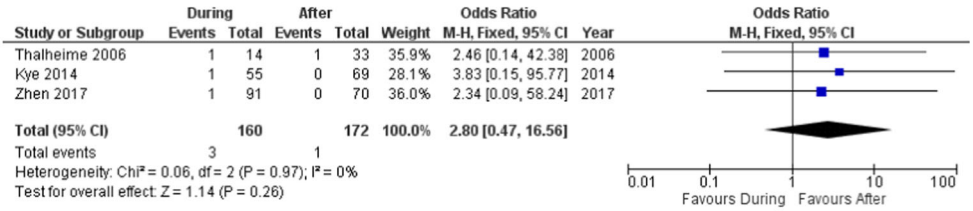
Sensitivity analysis Using random effects or fixed effects models did not affect the pooled effect size in any of the outcomes. The direction of pooled effect size remained unchanged when the OR, RR or RD was calculated.

Discussion

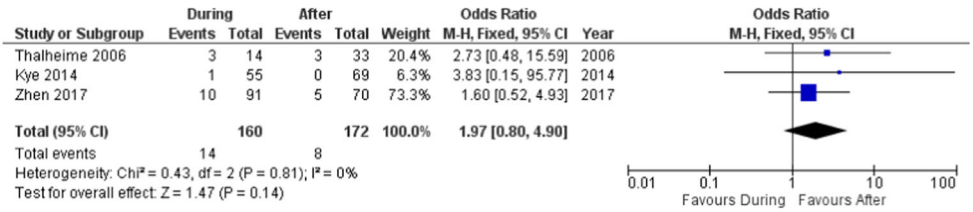
In view of the existence of controversies with regard to optimal timing of temporary loop ileostomy closure following rectal cancer surgery, we conducted a comprehensive systematic review and meta-analysis to compare outcomes of ileostomy closure during or after adjuvant chemotherapy. Our literature review identified 4 observational studies reporting a total of 436 patients of whom 183 underwent reversal of temporary loop ileostomy during adjuvant chemotherapy and the remaining 251 had reversal of temporary loop ileostomy after adjuvant chemotherapy. The meta-analysis of outcomes demonstrated no significant difference in overall



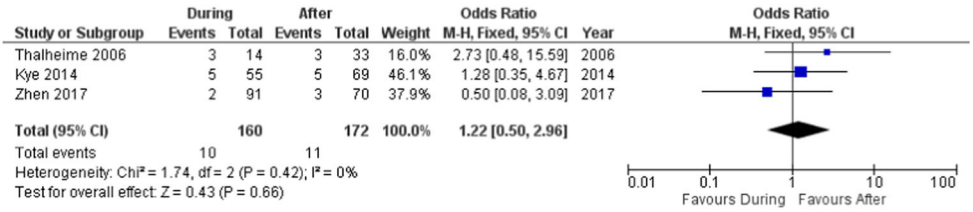
(a) Overall perioperative complications



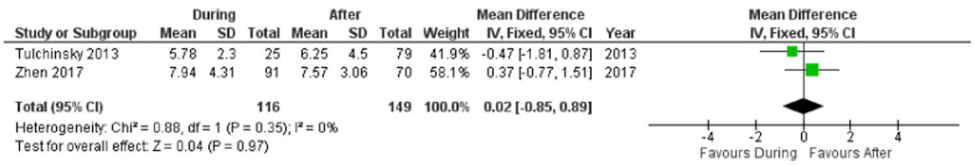
(b) Anastomotic leak



(c) Surgical site infection



(d) Ileus



(e) Length of hospital stay

Fig. 2 Forest plots of comparison of **a** overall perioperative complications, **b** anastomotic leak, **c** surgical site infection, **d** Ileus and **e** length of hospital stay. The solid squares denote the odds ratios (ORs) or mean difference (MD). The horizontal lines represent the 95% confidence intervals (CIs), and the diamond denotes the pooled effect size. M-H Mantel-Haenszel test

perioperative complications, anastomotic leak, SSI, ileus or length of hospital stay between two groups. The statistical between-study heterogeneity in all outcome analyses was low, making our conclusions robust.

Standardised adjuvant chemotherapy has been demonstrated to improve the disease-free survival and overall survival of rectal cancer patients [22]. Moreover, it has been recommended that adjuvant chemotherapy should be administered as soon as possible [23]. Every 4-week delay in the administration of adjuvant chemotherapy has been demonstrated to decrease overall survival of colorectal cancer patients by 14% [24]. Early closure of the protecting stoma during adjuvant chemotherapy can be complicated by anastomotic leakage or LAR syndrome leading to a substantial delay in the completeness of chemotherapy, the duration of which has been recommended not to exceed 6 months [13, 23]. However, there is no convincing evidence to suggest that closure of temporary loop ileostomy during adjuvant chemotherapy is associated with worse outcomes than that after chemotherapy. Recent meta-analyses have demonstrated that early closure of loop defunctioning ileostomy in patients undergoing distal colorectal resection has comparable outcomes with the delayed closure. However, the outcomes were not reported with respect to adjuvant chemotherapy [24, 25].

Only one of our included studies, Zhen et al. [18], evaluated the quality of life of their included patients. The authors investigated the quality of life with respect to body image, sexual function, sexual enjoyment and future perspectives and found no significant difference between the two groups. Nevertheless, it has been well reported that the loop ileostomies have a considerable negative impact on the quality of life and psychological well-being [7, 8, 26].

We did not find any difference in anastomotic leak or SSIs between reversal of ileostomy during or after adjuvant chemotherapy. Nevertheless, these findings might have been biased by some important confounding factors. The anastomotic leak may be dependent on the method the anastomosis is performed. However, the method of anastomosis was poorly reported by the included studies. With regard to the SSIs, it is not clear whether the included studies used linear skin closure or purse-string skin closure technique to close the stoma site. We have previously demonstrated that the risk of SSI is significantly lower when purse-string skin closure technique is used [27].

To our knowledge, no meta-analysis has evaluated the timing of temporary loop ileostomy closure with respect to adjuvant chemotherapy. Our meta-analysis of best available evidence (level 2) has demonstrated that temporary loop ileostomy closure during adjuvant chemotherapy following colorectal cancer resection is also comparable with the closure of ileostomy after adjuvant chemotherapy. However, no definitive conclusion can be drawn as there are several shortcomings associated with the available evidence. None of our included studies reported whether closure of ileostomy before chemotherapy significantly affected the completeness of chemotherapy. Moreover, the quality of life of the patients has not been assessed. The findings of an ongoing randomised controlled trial, CoCStom trial [13], which aims to evaluate optimal timing of stoma closure in the context of adjuvant chemotherapy, may provide stronger evidence in favour of either approach.

The limitations of our study should be taken into account when interpreting our findings. The current literature lacks randomised controlled trials, the gold standard study design for comparative studies, to provide high-quality evidence for or against stoma closure during or after adjuvant chemotherapy. The best available evidence comes mainly from a small number of observational studies which are inevitably subject to selection bias. Moreover, the small sample sizes of the included studies may subject our study findings to type 2 error. Considering the data provided by the included studies, we could not evaluate the quality of life and completeness of chemotherapy as an outcome. This, undoubtedly, would have had an important impact on the evaluation of the appropriateness of either approach. Furthermore, the included studies have not reported the method of anastomosis and stoma site closure which would bias our findings on anastomotic leak and SSI, respectively. Finally, the risk of bias was moderate in 2 studies which may bias our results in favour of an intervention.

Conclusions

Our meta-analysis of best available evidence demonstrated that temporary loop ileostomy closure during adjuvant chemotherapy following rectal cancer resection may be associated with comparable outcomes to the closure of ileostomy after adjuvant chemotherapy. However, the available evidence is too limited to help make definitive conclusions. The findings of this meta-analysis can encourage future research to concentrate on completeness of chemotherapy and quality of life as important outcomes which can potentially determine the appropriateness of either approach. Undoubtedly, high quality randomised trials with adequate sample sizes may provide stronger evidence in favour of either approach.

Author contribution Conception and design: Shahin H, RP
Literature search and study selection: Shahin H, Shahab H, JE
Data collection: Shahin H, Shahab H
Analysis and interpretation: Shahin H, Shahab H
Writing the article: Shahin H, Shahab H
Critical revision of the article: All authors
Final approval of the article: All authors
Statistical analysis: Shahin H, Shahab H

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

Table 3 Search operators and limits in the aforementioned databases

Search no.	Search strategy*
#1	MeSH descriptor: [loop iloestomy] explode all trees
#2	loop ileostomy: TI,AB,KW
#3	MeSH descriptor: [defunctioning] explode all trees
#4	defunctioning: TI,AB,KW
#5	MeSH descriptor: [stoma] explode all trees
#6	stoma: TI,AB,KW
#7	MeSH descriptor: [temporary ileostomy] explode all trees
#8	temporary ileostomy: TI,AB,KW
#9	MeSH descriptor: [protecting ileostomy] explode all trees
#10	protecting ileostomy: TI,AB,KW
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	reversal: TI,AB,KW
#13	closure: TI,AB,KW
#14	#12 OR #13
#15	chemotherapy: TI,AB,KW
#16	#11 AND #14 AND # 15

*This search strategy was adopted for following databases: MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL)

References

1. Meyer JE, Narang T, Schnoll-Sussman FH, Pochapin MB, Christos PJ, Sherr DL (2010) Increasing incidence of rectal cancer in patients aged younger than 40 years: an analysis of the surveillance, epidemiology, and end results database. Cancer 116:4354–4359
2. Gastinger I, Marusch F, Steinert R, Wolff S, Koeckerling F, Lippert H, Working Group 'Colon/Rectum Carcinoma' (2005) Protective defunctioning stoma in low anterior resection for rectal carcinoma. Br J Surg 92(9):11137–11142
3. Heald RJ (1995) Total mesorectal excision is optimal surgery for rectal cancer: a Scandinavian consensus. Br J Surg 82(10):1297–1299
4. Nicholls RJ, Hall C (1996) Treatment of non-disseminated cancer of the lower rectum. Br J Surg 83(1):15–18
5. Matthiessen P, Hallböök O, Rutegård J, Simert G, Sjödahl R (2007) Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 246(2):207–214
6. Montedori A, Cirocchi R, Farinella E, Sciannameo F, Abraha I (2010) Covering ileo- or colostomy in anterior resection for rectal carcinoma. Cochrane Database Syst Rev 12(5):CD006878
7. Bakx R, Busch OR, Bemelman WA, Veldink GJ, Slors JF, van Lanschot JJ (2004) Morbidity of temporary loop ileostomies. Dig Surg 21(4):277–281
8. Tsunoda A, Nakao K, Hiratsuka K, Tsunoda Y, Kusano M (2007) Prospective analysis of quality of life in the first year after colorectal cancer surgery. Acta Oncol 46(1):77–82
9. Perdawid SK, Andersen OB (2011) Acceptable results of early closure of loop ileostomy to protect low rectal anastomosis. Dan Med Bull 58:A4280
10. Alves A, Panis Y, Lelong B, Dousset B, Benoist S, Vicaut E (2008) Randomized clinical trial of early versus delayed temporary stoma closure after proctectomy. Br J Surg 95:693–698
11. Hindenburg T, Rosenberg J (2010) Closing a temporary ileostomy within two weeks. Dan Med Bull 57:A4157
12. Krand O, Yalti T, Berber I, Tellioglu G (2008) Early vs. delayed closure of temporary covering ileostomy: a prospective study. Hepatogastroenterology 55:142–145
13. Sandra-Petrescu F, Herrle F, Hinke A, Rossion I, Suelberg H, Post S, Hofheinz RD, Kienle P (2015) CoCStom trial: study protocol for a randomised trial comparing completeness of adjuvant chemotherapy after early versus late diverting stoma closure in low anterior resection for rectal cancer. BMC Cancer 15:923
14. Oliphant R, Czerniewski A, Robertson I, McNulty C, Waterston A, Macdonald A (2015) The effect of adjuvant chemotherapy on stoma-related complications after surgery for colorectal cancer: a retrospective analysis. J Wound Ostomy Continence Nurs 42(5):494–498
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339:b2700
16. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed Feb 2018
17. Higgins JP, Altman DG (eds). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S (eds). Cochrane handbook for systematic reviews of interventions. Version 5.0.1 [updated September 2008]. Available at: http://hiv.cochrane.org/sites/hiv.cochrane.org/files/uploads/Ch08_Bias.pdf. Accessed Feb 2018
18. Zhen L, Wang Y, Zhang Z, Wu T, Liu R, Li T, Zhao L, Deng H, Qi X, Li G (2017) Effectiveness between early and late temporary ileostomy closure in patients with rectal cancer: a prospective study. Curr Probl Cancer 41(3):231–240

19. Kye BH, Kim HJ, Kim JG, Cho HM (2014) Is it safe the reversal of a diverting stoma during adjuvant chemotherapy in elderly rectal cancer patients? Int J Surg 12(12):1337–1341
20. Tulchinsky H, Shacham-Shmueli E, Klausner JM, Inbar M, Geva R (2014) Should a loop ileostomy closure in rectal cancer patients be done during or after adjuvant chemotherapy? J Surg Oncol 109(3): 266–269
21. Thalheimer A, Bueter M, Kortuem M, Thiede A, Meyer D (2006) Morbidity of temporary loop ileostomy in patients with colorectal cancer. Dis Colon Rectum 49:1011–1017
22. Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S (2012) Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev 14(3):CD004078
23. National Comprehensive Cancer Network. Network NCC rectal cancer, NCCN guidelines 2015; Version 3
24. Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM (2011) Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA 305(22):2335–2342
25. Menahem B, Lubrano J, Vallois A, Alves A (2018) Early closure of defunctioning loop ileostomy: is it beneficial for the patient? A meta-analysis. World J Surg 42(10):3171–3178
26. O'Leary DP, Fide CJ, Foy C, Lucarotti ME (2001) Quality of life after low anterior resection with total mesorectal excision and temporary loop ileostomy for rectal carcinoma. Br J Surg 88:1216–1220
27. Hajibandeh S, Hajibandeh S, Kennedy-Dalby A, Rehman S, Zadeh RA (2018) Purse-string skin closure versus linear skin closure techniques in stoma closure: a comprehensive meta-analysis with trial sequential analysis of randomised trials. Int J Color Dis 33(10): 1319–1332