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COLOR IV: a multicenter randomized clinical trial comparing intracorporeal and extracorporeal ileocolic anastomosis after laparoscopic right colectomy for colon cancer

Si Wu[1] · Pengyu Wei[1] · Jiale Gao[1] · Wenlong Shu[1] · Hanzheng Zhao[1] · Hendrik Bonjer[2] · Jurriaan Tuynman[2] · Hongwei Yao[1] · Zhongtao Zhang[1] · For the COLOR IV study group

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Abstract

Introduction Right-sided colon cancer is a prevalent malignancy. The standard surgical treatment for this condition is laparoscopic right hemicolectomy, with ileocolic anastomosis being a crucial step in the procedure. Recently, intracorporeal ileocolic anastomosis has garnered attention for its minimally invasive benefits. However, there remains a paucity of rigorously designed, large-scale, international multicenter randomized controlled trials to definitively assess the safety and efficacy of intracorporeal ileocolic anastomosis in laparoscopic right hemicolectomy for right-sided colon cancer.

Methods This study is an international, multicenter, randomized, controlled, open-label, non-inferiority trial designed to compare the safety and efficacy of intracorporeal versus extracorporeal ileocolic anastomosis in patients with right-sided colon cancer undergoing right hemicolectomy. The primary endpoint is the anastomotic leakage rate within 30 days post-surgery. The main secondary endpoint is the 3-year disease-free survival rate post-surgery. A comprehensive quality assurance protocol will be established before the trial begins, including CT review, pathological evaluation, and the standardization and assessment of surgical techniques.

Discussion This study aims to evaluate the safety and efficacy of intracorporeal ileocolic anastomosis following right hemicolectomy in patients with right-sided colon cancer. The anticipated outcome is that intracorporeal ileocolic anastomosis will show an anastomotic leakage rate and a 3-year disease-free survival rate comparable to those of extracorporeal anastomosis, while offering the added benefit of faster postoperative recovery.

Si Wu, Pengyu Wei, Jiale Gao, Wenlong Shu, and Hanzheng Zhao shared first authorship and contributed equally to this work.

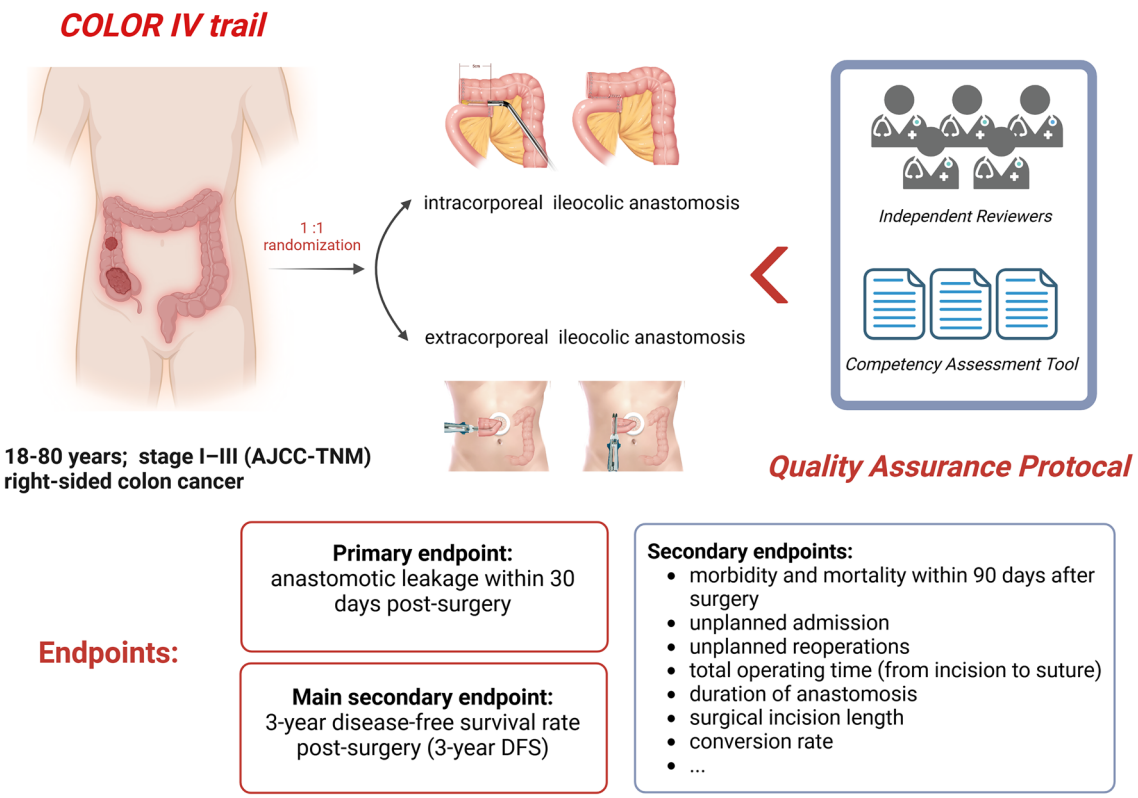
✉ Hongwei Yao
yaohongwei@ccmu.edu.cn

✉ Zhongtao Zhang
Zhangzht@ccmu.edu.cn

[1] State Key Lab of Digestive Health, Department of General Surgery, National Clinical Research Center for Digestive Diseases, Beijing Friendship Hospital, Capital Medical University, No. 95 Yongan Road, Xicheng District, Beijing 100050, China

[2] Department of Surgery, Amsterdam University Medical Center, Amsterdam, The Netherlands

Graphical abstract



Keywords Colon cancer · Laparoscopic · Intracorporeal ileocolic anastomosis · Anastomotic leakage

Colorectal cancer (CRC) is the third most common malignancy in men, following lung and prostate cancer, and the second most common in women, after breast cancer [1]. Annually, approximately 1.881 million new cases of CRC are diagnosed, and the disease leads to 916,000 deaths worldwide [1]. Right hemicolectomy (RHC) is the standard surgical treatment for patients with right-sided colon cancer. When compared to open surgery, laparoscopic-assisted procedures are oncologically equivalent, with comparable recurrence rates, disease-free survival (DFS), and overall survival (OS). Additionally, laparoscopic-assisted surgery offers significant advantages, including reduced postoperative complications, lower mortality rates, decreased pain, faster postoperative recovery, and improved short-term outcomes [2, 3].

Ileocolonic anastomosis is a critical step in RHC, with extracorporeal ileocolic anastomosis (EIA) being the most commonly used approach [4, 5]. Laparoscopic right hemicolectomy (LRH) with intracorporeal ileocolic anastomosis (IIA), first reported in 1992 [6], offers several potential advantages. These include reduced torsion and traction on the mesentery and colon, improvement of blood supply of anostomosis, and minimized skin incision length, all of which can enhance postoperative recovery. However, this technique also has notable drawbacks, such as an increased risk of intra-abdominal infections and a steep learning curve, which may contribute to higher rates of postoperative complications, particularly anastomotic leakage (AL) [7–10]. Currently, high-level research evidence on its impact on both short-term and long-term outcomes remains limited.

Most studies comparing complications between IIA and EIA lack large sample sizes and rigorous quality control, leading to widely varying results. Anastomotic leakage is a significant complication following RHC, serving as a risk factor for both mortality and postoperative recurrence. Reported AL rates vary considerably across studies. A meta-analysis involving 4450 patients indicated a higher AL rate in the EIA group compared to the IIA group following minimally invasive RHC [11]. However, a randomized controlled trial (RCT) by Allaix et al. reported an AL rate of 8.6% in the IIA group versus 2.9% in the EIA group [12]. Beyond AL, some reports suggest that IIA may offer advantages in reducing other complications, such as surgical site infections (SSI) and incisional hernias [11–13]. In terms of oncological

outcomes, Hanna's study demonstrated similar 5-year overall survival and disease-free survival rates between the IIA and EIA groups [14]. These findings underscore the critical need for a well-designed RCT with standardized surgical protocols, comprehensive training programs, and rigorous assessment criteria to ensure that participating surgeons possess the requisite skills. This study aims to validate the safety and efficacy of the IIA technique in LRH.

Materials and methods

The COLOR IV trial is an international, multicenter, randomized, controlled, open-label, non-inferiority trial comparing IIA with EIA in patients undergoing RHC for right-sided colon cancer (Fig. 1).

Eligibility

The COLOR IV trial aims to enroll a total of 1158 patients, aged 18–80 years, who have been histologically or cytologically diagnosed with right-sided colon cancer involving the cecum, ascending colon, or the proximal one-third of the transverse colon. Eligible patients will have stage I–III colon cancer according to the 8th edition of the AJCC-TNM classification. These patients must be suitable candidates for LRH, including extended right hemicolectomy with primary anastomosis, and must provide informed consent in accordance with local regulations.

Exclusion criteria include the presence of T4b tumors identified by CT scan, histological evidence of malignancies other than adenocarcinoma, a history of other malignancies (except for adequately treated basal cell carcinoma of the skin or in situ carcinoma of the cervix uteri), prior colorectal resection, or synchronous multiple colorectal malignancies. Patients requiring emergency surgery, those planning synchronous abdominal organ resections, robot-assisted surgery or those planning natural orifice specimen extraction surgery, as well as pregnant women, are also excluded. Additionally, patients receiving neoadjuvant therapy are not eligible for this trial. Individuals with Familial Adenomatous Polyposis (FAP), active Crohn's disease, active ulcerative colitis, or absolute contraindications to general anesthesia or prolonged pneumoperitoneum are also ineligible for participation in the study (Fig. 2).

Before participating in the COLOR IV study, all centers must undergo a rigorous quality assurance program to ensure adherence to study protocols and accuracy in data collection. Enrollment in the study is competitive, with recruitment ceasing once the target number of patients is reached. The study is planned to span 7 years in total, with 4 years allocated for patient enrollment and 3 years for follow-up.

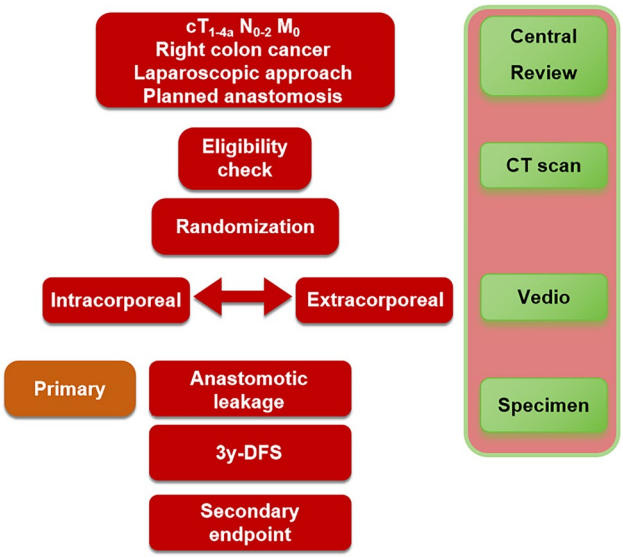


Fig. 1 Flowchart of the study design

Randomization

The study will randomly assign all eligible patients to one of two procedures in a 1:1 ratio. Patients may be informed of their allocation. Randomization will be managed through a centralized system, which will ensure balance based on tumor stage (AJCC 8th edition: stage I/II/III), region (Asia/Europe), and BMI (BMI < 30 kg/m^2/BMI ≥ 30 kg/m^2). Researchers have entered this information into the central evaluation system, which will generate randomization codes to ensure patients are assigned to either the IIA or EIA groups in a 1:1 ratio.

Surgical procedure

In the intervention arm of the study, LRH with IIA requires complete laparoscopic dissection of the mesocolon. The extent of colon resection is determined based on tumor location, excluding ileocecal resection. D2 or D3/CME dissection is optional. After fully mobilizing the colon and mesentery, the terminal ileum and transverse colon are transected using a laparoscopic linear stapler. A stapled side-to-side anastomosis is mandatory, with the option of performing either isoperistaltic or antiperistaltic anastomosis. All anastomotic procedures are performed laparoscopically. For incisions, a Pfannenstiel or periumbilical incision is recommended, with the mandatory use of an incision protector.

In the control arm, LRH with EIA follows similar procedures for mobilization and dissection of the mesocolon. Subsequently, the mobilized colon and terminal ileum are brought out through an upper mid-line incision using a mandatory wound protector. The colon and terminal ileum are

Inclusion criteria
1) Histological or cytological diagnosis of right colon cancer (cecum, ascending colon or proximal 1/3 of the transverse colon)
2) Age of I8-80 years
3) Stage I-III disease according to the 8th AJCC-TNM classification
4) Intention for (extended) right hemicolectomy with primary anastomosis
5) Informed consent according to local protocols
Exclusion criteria
1) cT4b/multivisceral resection
2) Malignancy other than adenocarcinoma at histological examination
3) Other malignancies in medical history, except adequately treated basal cell carcinoma of the skin or in situ carcinoma of the cervix uteri
4) Prior colon and/or rectum resection or multiple colorectal tumours
5) Emergency surgery
6) Neoadjuvant therapy
7) Planned synchronous abdominal organ resections
8) Planned natural orifice specimen extraction surgery
9) Pregnancy
10)Familial Adenomatosis Polyposis Coli (FAP), active Crohn's disease or active ulcerative colitis
11)Absolute contraindication to general anesthesia or prolonged pneumoperitoneum

Fig. 2 Details of inclusion and exclusion criteria

dissected distally to the specimen using a stapling device. A stapled side-to-side anastomosis is also mandatory.

In both the experimental and control groups, techniques such as isoperistaltic or antiperistaltic anastomosis, enterotomy, anastomosis reinforcement, and mesenteric defect closure are not mandatory but can be selected by the surgeon based on their preferences and the specific circumstances of the case. Surgeons are encouraged to adhere to their usual practices to ensure procedural safety and maintain study protocol consistency (Fig. 3).

Conversion to open surgery is defined as a decision made by the surgeon due to technical challenges, concerns regarding patient safety, or oncological safety, necessitating a switch from a laparoscopic to an open surgical approach. Conversion to EIA occurs when the surgeon, faced with technical difficulties or complications that prevent the completion of IIA, opts to perform a conventional EIA instead.

COLOR IV trial quality assurance

To ensure both surgical quality and the adherence of centers to the study protocol, including recruitment processes and data collection, a comprehensive *Quality Assurance Protocol* has been developed and will be implemented prior to the commencement of the trial.

To assess surgical quality, a *Competency Assessment Tool* (CAT) has been developed specifically for evaluating technical and oncological aspects of LRH with IIA and EIA within the framework of the COLOR IV trial. The CAT will adopt the standards used by the Right study [15] and be used to select surgeons for participation in the trial and to monitor adherence to established surgical quality standards throughout the study. The development of this CAT involved applying a Delphi methodology with input from a panel of internationally recognized colorectal surgery experts specializing in LRH techniques. A technical manual and operation logbook were created based on the consensus reached through this process. The CAT for LRH was then validated to ensure it meets rigorous reliability and validity criteria before its implementation in both the pre-trial and main trial phases of the study.

Before entering the COLOR IV trial, participating centers must meet specific criteria, including treating a minimum of 50 patients annually with right-sided colon cancer and completing a dedicated training program that includes supervised training by a proctor. Centers with expertise in LRH with IIA may participate in hands-on training and proctoring sessions.

To ensure entry quality into the trial, each participating center must recruit three consecutive cases: one LRH with EIA and two LRH with IIA. These cases must provide

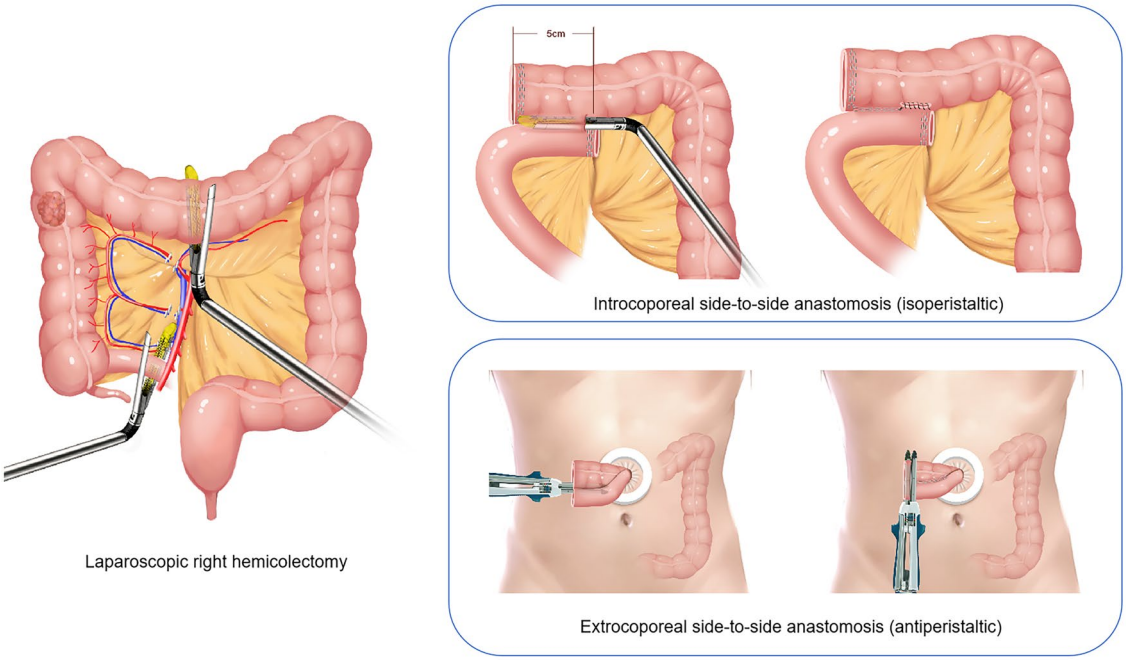


Fig. 3 The surgical procedure of anastomosis in the intervention arm (intracorporeal ileocolic anastomosis) and the control arm (extracorporeal ileocolic anastomosis): the terminal ileum and transverse colon are transected using a laparoscopic linear stapler and side-to-side anastomosis is mandatory in both arms

unedited operative videos and baseline characteristics (such as gender, age, BMI, tumor location, and TNM stage) for assessment. Surgical performance will be evaluated by two independent reviewers using the CAT. Surgeons who do not initially meet entry criteria will receive additional training through the COLOR IV program and may be reassessed. Since IIA is routinely performed in the participating hospitals, the surgical quality assurance before the COLOR IV trial does not involve randomization, and the data collected are not used in the trial. The operative videos of the three patients collected for quality assurance purposes before the trial commencement are accepted without specific informed consent. However, informed consent is required from all patients participating in the COLOR IV trial. During the trial, the first three cases performed by each surgeon will undergo extensive monitoring to ensure compliance with the COLOR IV protocol, including data collection and treatment procedures. Clinical data, including CT scans and pathology reports, will be centrally reviewed using the COLOR IV secure digital case record form, with compliance monitored via a checklist. Automated reminders will be sent to local trial coordinators for timely submission of requested information to minimize follow-up delays. To monitor surgical quality throughout the trial, participating surgeons must use standardized operation notes to document procedures and justify any deviations from the protocol. Unedited videos of each operation, whether IIA or EIA after LRH, will be submitted and evaluated using the CAT to assess the learning curve within the trial. Specifically, each surgical step will be evaluated in four aspects: exposure, execution, adverse events, and end-product quality. Each component will be scored on a scale from 1 to 4, representing execution from risky to skilled.

Furthermore, perioperative treatment strategies for patients must be determined following multidisciplinary discussions. Prior to surgery, each center must adhere to protocols for deep vein thrombosis prophylaxis, antibiotic prophylaxis, and enhanced recovery programs, ensuring consistent preoperative care across both treatment groups [16]. During surgery, standardized anesthesia protocols are mandatory, with a preference against epidural anesthesia [17]. Postoperative care and rehabilitation should align with enhanced recovery principles, including multimodal analgesic regimens, early resumption of oral intake based on patient tolerance, early mobilization, and discontinuation of prophylactic antibiotics within 24 h [17]. Lastly, postoperative adjuvant therapy is recommended in accordance with international guidelines from organizations such as NCCN, ASCO, ESMO, and NICE.

Follow-up

During the postoperative hospital stay, detailed records of AL and other complications must be maintained. Patients

should be followed up within 1 month (25–35 days) after surgery, with thorough investigation of any complications that arise after discharge. Key complications include AL, chylous ascites, gastrointestinal bleeding, intra-abdominal bleeding, intestinal obstruction, postoperative diarrhea, surgical site infection (SSI), thrombotic events, cardiovascular events, pulmonary infection, urinary tract infection, among others. The severity of complications is graded using the Clavien–Dindo classification.

Long-term follow-up is required at least every 6 months for up to 3 years according to international guidelines (NCCN, ASCO, ESMO, NICE), with more frequent follow-up as needed based on clinical indication or physician's discretion. Recommended assessments include chest, abdominal, and pelvic CT scans, as well as carcinoembryonic antigen (CEA) testing. Colonoscopy is recommended at 1 year post-surgery and subsequently as clinically indicated; however, PET-CT is not deemed necessary unless specifically indicated for suspected recurrence. In cases where recurrence is suspected, further imaging and pathological examinations should be performed.

Mandatory abdominal and pelvic CT scans at 1 year and 3 years post-surgery should be uploaded for centralized review to assess for recurrence and herniation. Patients' quality of life and functioning will be assessed using electronic or paper-based questionnaires, including EQ-5D-5L (Euroqol), Global Quality of Life (EORTC-QLQ-C30-QL2), and Global Quality of Life (EORTC-QLQ-CR29). These validated instruments will evaluate post-treatment functional outcomes at admission, and at 3, 6, and 12 months postoperatively. EQ-5D-5L is a simple, generic tool assessing health-related quality of life across five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) on a 5-point scale ranging from "no problem" to "extreme problems". EORTC-QLQ-C30 and EORTC-QLQ-CR29 are comprehensive questionnaires evaluating overall quality of life, functioning, and symptoms in colorectal cancer patients, encompassing 30 and 29 items, respectively.

Minor complications are recorded in routine case report forms, while serious adverse events (SAEs) require completion of a specific SAE report form. In cases of recurrence (local or distant), a recurrence report form must be completed and submitted electronically to the coordinating center within 2 weeks of detection. Follow-up for recurrent disease should continue for at least 3 years after diagnosis or until death, documenting recurrences and treatment plans in the appropriate forms. All adverse events are monitored until resolution or stabilization, potentially necessitating additional tests, procedures, or referral to specialists as warranted.

Endpoints

The primary endpoint of this trial is AL occurring within 30 days after surgery. A consensus on the definition, diagnosis, and grading criteria for AL following RHC has been reached through a nationwide multicenter Delphi survey [18]. Anastomotic leakage is characterized by an intestinal wall defect at the anastomotic site, leading to communication between intra- and extraluminal compartments. Clinical signs of AL may include fever (> 37.5 ℃), abdominal pain unrelated to the incision, sepsis, and peritonitis. Laboratory indicators such as elevated white blood cell counts (WBC > 12×10^9/L), procalcitonin (PCT > 0.5 ug/L), and C-reactive protein (CRP > 50 mg/L) three days after surgery are relevant. According to this standard, after the third postoperative day, the decision to continue daily monitoring, switch to alternate-day monitoring, or discontinue laboratory tests will be based on the patient's complaints, symptoms, signs, and the physician's clinical judgment. If any symptoms, signs, or laboratory tests described in the manuscript suggest the possibility of anastomotic leakage, a pelvic and abdominal CT scan is essential to determine its presence. AL can be confirmed by fecal drainage fluid, extravasation of contrast agent on CT scan, presence of air bubbles around the anastomosis on CT, or anastomotic dehiscence during secondary laparoscopy or laparotomy. Anastomotic leakage severity should be graded both using the International Study Group of Rectal Cancer and Clavien–Dindo classifications. It is crucial to differentiate between clinically suspected AL, necessitating radiologic evaluation, and confirmed AL. If the patient is doing well, a CT scan is not mandatory within the first 30 days postoperatively.

The main secondary endpoint is 3-year DFS, defined from the surgery date to recurrence, metastasis, or death. Local recurrence refers to tumor regrowth at the surgical site, confirmed by radiological (CT or PET–CT) or CEA testing, supported by pathology. Distant metastasis indicates tumor recurrence outside the primary site (e.g., liver, lung, bone), diagnosed radiologically without necessarily needing pathological confirmation.

Secondary endpoints include morbidity and mortality within 90 days after surgery, unplanned admission (defined as unplanned readmission for the same or related illness within 30 days of discharge), and unplanned reoperations (defined as unplanned reoperations performed by the patient for various reasons during the same hospital stay), total operating time (from incision to suture), duration of anastomosis (from opening of intestine to closing the intestine), surgical incision length, conversion rate (defined as conversion to either open surgery or to EIA), pain score (VAS score) 1–3 days after surgery, time to first flatus and stool passage after surgery, time to resume liquid diets, the length of the patient's hospital stay after surgery, surgical specimen

quality (the Benz classification [19]), incision herniation within 1 year after surgery, 3-year overall survival after surgery and health-related quality of life scores.

Statistics and data analysis

The primary endpoint is AL within 30 days after surgery. The AL rate was set to 2% in the both groups, and an increase in the incidence of AL of 3% was considered inferior. The one-sided significance level was 0.025, the power was 0.9. The dropout rate was 20%, and taking into account the post-randomization analysis (dropout 5%), the total sample size was 1158. There will be 579 cases in the IIA group and 579 cases in the EIA group. The main secondary endpoint is 3-year DFS rate. We pre-calculated the sample size with this as the endpoint. The 3-year DFS rate is set to 80% in the both groups, and a decrease of 8% was considered inferior. The one-sided significance level was 0.025, the power was 0.8. The dropout rate was 20%. The calculated sample size is 994, which means the sample size of this study is sufficient to validate this endpoint.

Baseline numerical data will be described using mean, standard deviation, or median with interquartile range, and baseline categorical data will be presented as percentages. All comparative analyses will be performed on an "intention-to-treat" basis. Therefore, patients randomized to the IIA group and switched to the EIA group will be analyzed as the EIA. Patients randomized to the EIA group and switched to the IIA will be analyzed as the IIA group. Postoperative complication rates will be tested by the chi-square test. Length of surgery, length of hospital stay, postoperative recovery time of intestinal function, pain score, etc. will be analyzed by *t* test or analysis of variance. Local recurrence rate, disease-free and overall survival will be compared using log-rank test. Exploratory analysis of complication rates by various baseline factors will be performed by multiple Cox regression.

Monitoring, audit and inspection

Governors will be appointed to monitor trial progress on site, as frequently as seen necessary. The medical ethical review board of the coordinating center (VU University Medical Centre) will register the trial at the clinical research bureau (CRB).

Trial registration

The trial has been registered at http://clinicaltrials.gov (NCT05493033).

Discussion

Laparoscopic colectomy has increasingly become the preferred treatment for both benign and malignant diseases of the right colon due to its favorable clinical outcomes and lower costs compared to open resection [3, 20, 21]. Recently, RHC for colon cancer has also become more common. Methods for restoring intestinal continuity after RHC include IIA and EIA. Currently, there are no universally accepted guidelines on which anastomotic technique is superior in terms of minimizing complications and achieving optimal short- and long-term outcomes, as reported studies show varying results. The incidence of AL after LRH varies widely, with reported rates ranging from 1 to 32% [22–26]. Retrospective studies have reported AL rates between 4 and 8% [4, 27, 28], while RCTs typically report lower rates, ranging from 1 to 3% [3, 26, 29]. Some meta-analyses and RCTs suggest no significant difference in AL incidence between IIA and EIA techniques [3, 13, 30, 31]. For example, Xu et al. reported an AL rate of only 1% with strict screening conditions [26], while Yamamoto et al. reported a 3.6% AL rate based on patient photographs [29]. Other RCTs have reported higher AL rates, although these were not statistically significant compared to EIA. Vignali et al. observed a 6.6% AL rate in the IIA group [32], and RCTs by Bollo et al. [33] and Manuel et al. [30] reported AL rates of 4% and 4.9%, respectively. Allaix et al. even reported an 8.6% AL rate [12]. The variability in AL rates across RCTs highlights the limited sample sizes and, more importantly, the technical complexity of IIA. This underscores the need for preoperative training to ensure the safety of the procedure. Therefore, our study implements a strict surgical quality control program to ensure the safety of the operation and anastomosis, with the AL rate in this study set at 2%.

Overall, there is a clear need for large-scale studies with standardized definitions of AL and rigorous quality control measures to better understand complications following RHC, particularly regarding AL. This approach would help provide clearer insights into the true incidence, risk factors, and optimal management strategies for AL in this surgical context.

As a succession of large international multicenter randomized controlled trial series, the COLOR IV trial is a non-inferiority design study comparing the survival and prognosis of patients with right-sided colon cancer between EIA and IIA. Compared with the other studies reported, with a sample size of 1158 cases, it has developed a quality assurance protocol and agreed surgical quality standards to ensure surgical quality. The surgical performance will be assessed by two independent reviewers using CAT and it will avoid the influence of learning

curve. What's more, one designated specialized pathologist will handle all resected specimens from each center. In addition, consensus on the definition of AL has been achieved and it has been used in the research via a Delphi study [18]. Using the strict quality assurance, it is expected to demonstrate the safety of IA in terms of AL and DFS, as well as advantages in postoperative intestinal function recovery (postoperative defecation, postoperative pain, length of hospital stay), and incidence of incisional hernia one year after surgery. Furthermore, with the use of CAT, the trial will potentially contribute to the analysis of the relationship between learning curve and outcomes mentioned above which is a critical but less focused problem in the recent studies.

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Declarations

Disclosures Drs. Si Wu, Pengyu Wei, Jiale Gao, Wenlong Shu, Hanzheng Zhao, Hendrik J. Bonjer, Jurriaan A. Tuynman, Hongwei Yao, and Zhongtao Zhang have no conflicts of interest or financial ties to disclose.

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