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Influence of the ligation sequence of the inferior mesenteric artery and vein on circulating tumor cells in laparoscopic rectal cancer surgery: a prospective pilot study

Tao Pan¹, Chang-bo Nie¹, Chao Liu¹ and Hai Hu^{1*}

Abstract

Background There is no regulation in the current guidelines on the sequence of ligation of the inferior mesenteric artery and vein during rectal cancer surgery owing to a lack of sufficient evidence. Circulating tumor cells (CTCs) in peripheral blood can be used as potential indicators for predicting prognosis in colorectal cancer patients. This study aims to explore the feasibility of different ligation sequences for the inferior mesenteric vessels and their potential influence on CTCs.

Methods This pilot study involved 29 stage I-III rectal adenocarcinoma patients undergoing laparoscopic surgery. Patients were allocated into two groups based on the sequence of vascular ligation: vein-first (V-first) and artery-first (A-first). The primary objective was to assess the impact of the ligation sequence on peripheral blood CTC levels pre- and post-operatively. Secondary outcomes included intraoperative complications, surgical duration, blood loss, and number of lymph nodes harvested, and postoperative complications. The study was approved by the ethics committee of our hospital (SCCHEC-02-2024-102), and all patients provided informed consent.

Results No significant differences were found between the two groups regarding surgical duration, blood loss, lymph nodes harvested, or postoperative complications. A reduction in CTCs postoperatively was observed in 36% of patients in the V-first group, in comparison to 20% in the A-first group.

Conclusion Both A-first and V-first ligation sequences are viable and safe options in laparoscopic rectal cancer surgery. The V-first approach may be more effective in reducing levels of CTCs in peripheral blood. Further randomized studies are warranted to explore these findings comprehensively.

Keywords Rectal cancer, Inferior mesenteric vessel, Circulating tumor cell, Surgical outcome

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Introduction

Colorectal cancer (CRC) ranks third in terms of incidence and mortality among all cancers [1]. Surgery continues to be the cornerstone for resectable rectal cancer [2, 3]. During the past two decades, outcomes have remarkably improved mostly owing to the introduction of total mesorectal excision (TME) [4]. However, one persisting concern is the potential for malignant tumor manipulation during surgery to enhance the shedding of tumor cells into the bloodstream, thereby possibly increasing the risk of distant metastases [5, 6]. A previous randomized study failed to confirm the superiority of the 'no touch' technique in colon cancer [7]. Furthermore, there has been no research on how the sequence of ligation of the inferior mesenteric vessels affects patient survival. Theoretically, ligating the effluent vein first could reduce the risk of tumor cell dissemination [8], but this approach is not yet standardized due to insufficient evidence to guide clinical practice.

In light of these uncertainties and the emerging role of circulating tumor cells (CTCs) as prognostic markers for postoperative recurrence and survival in CRC patients [9–12], our study was designed to investigate the impact of the ligation sequence of inferior mesenteric artery and vein on the levels of CTCs in peripheral blood, aiming to provide preliminary evidence for the next phase of a randomized controlled trial.

Materials and methods

Ethical issue

The ethics committee of Sichuan Cancer Hospital reviewed and approved this trial (SCCHEC-02-2024-102). All eligible participants and their legal surrogates were fully informed of the potential risks and benefits of the interventions in each group. All patients in the study signed an informed consent form.

Study design

Patients were divided into two groups based on the sequence of vascular ligation: the Vein-first Group (V-first), prioritizing ligation of the inferior mesenteric vein, and the Artery-first Group (A-first), prioritizing ligation of the inferior mesenteric artery. Given the exploratory nature of this pilot study, a non-random sequential enrollment strategy was employed. This approach is often used in early-phase feasibility studies where the primary objective is to assess the safety and viability of interventions before conducting more rigorous randomized trials. The non-random sequential method allowed for efficient grouping based on the timing of admission for surgery, and it has been successfully applied in similar research contexts [13, 14].

Study population

From April 2022 to February 2023, patients undergoing radical laparoscopic rectal cancer surgery in our medical team were prospectively enrolled in the study.

The inclusion criteria were as follows: (1) age: 18–75 years; (2) histopathologically confirmed as rectal adenocarcinoma (tumor located within 15 cm from the anal verge at colonoscopy); (3) patients with a stage I–III rectal cancer eligible for surgery and R0 resection is expected, patients with pelvic lateral lymph nodes metastasis are ineligible; (4) ECOG score: 0–1; (5) ASA score: I/II/III; (6) laparoscopic surgery; (7) signed informed consent.

The exclusion criteria included: (1) patients who have received preoperative treatment (such as preoperative radiotherapy and chemotherapy); (2) receiving transanal total mesorectal excision (taTME), specimen extraction through natural lumen (NOSES) or endoscopic tumor resection; (3) recurrent rectal cancer; (4) simultaneous or metachronous colorectal cancer; (5) malignant tumors of other organs in the past 5 years or at the same time; (6) the results of preoperative physical examination and imaging examination showed that: (a) the tumor involved the surrounding organs and required combined organ resection; (b) distant metastasis; (c) could not be resected at R0; (7) pregnant or lactating women; (8) patients with severe mental disorder; (9) it is not suitable for patients undergoing laparoscopic surgery (such as extensive adhesion caused by previous abdominal surgery or inability to tolerate artificial pneumoperitoneum); (10) history of unstable angina pectoris or myocardial infarction in the past 6 months; (11) history of cerebrovascular accident in the past 6 months; (12) systemic administration of corticosteroids within 1 month before enrollment; (13) taking folic acid related drugs within half a year before operation; (14) severe cardiac insufficiency (FEV1 < 50% of predicted values); (15) emergency surgery.

The exit criteria included: (1) Simultaneous ligation of the inferior mesenteric artery and vein during surgery, or the order of ligation cannot be distinguished; (2) Patients with distant metastases found during surgical exploration or confirmed by postoperative pathological examination. The patient enrollment flowchart is indicated in Fig. 1.

Clinicopathological characteristics

All clinical data was prospectively collected. Clinicopathological characteristics reported in the study included demographic parameters (age, sex, American Society of Anesthesiology (ASA) score, and body mass index (BMI)), preoperative serum CEA level (ng/ml), surgery type, intraoperative complications, surgical duration (min), blood loss (ml), tumor size (cm), lymph nodes harvested, pathological tumor stage (pT), pathological node stage (pN), pathological TNM stage (pTNM), lymphovascular invasion, neural invasion, tumor differentiation,

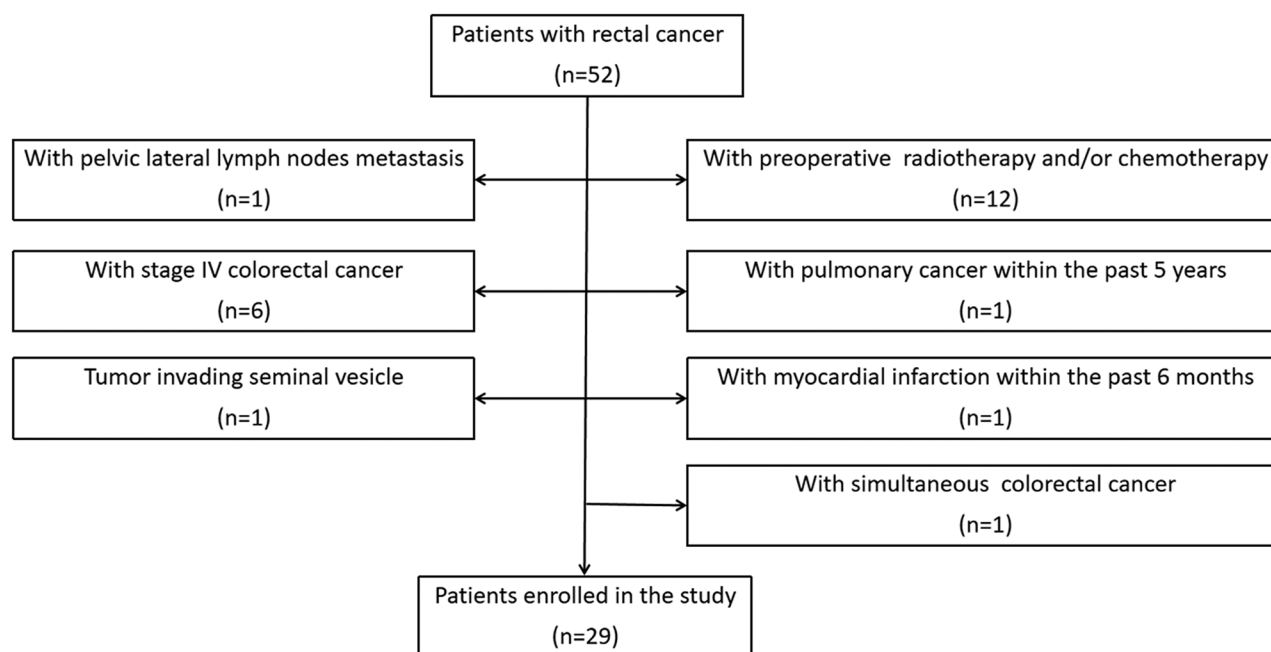


Fig. 1 Patient enrollment flowchart

MMR status, adjuvant chemotherapy, adjuvant radiotherapy, and postoperative complications. The clinicopathologic classification was determined according to the eighth edition of the American Joint Committee on Cancer (AJCC) Staging Manual [15]. The postoperative complications were graded according to the Clavien–Dindo classification [16].

Endpoints

The primary endpoint of the study was the change of CTC levels before and after surgery. When the CTC levels measured (preoperative and postoperative) differ by 15% or more, it is considered that there is a difference between the two results. The secondary endpoints were surgery-related outcomes (intraoperative complications, duration of the surgery, volume of blood loss, and number of lymph nodes harvested) and postoperative complications.

Surgical Technique

In this prospective cohort study, all surgical interventions were conducted by a consistent team comprised of Professor Chao Liu, Dr. Hai Hu, and Dr. Tao Pan. This uniform approach ensured that all procedures were performed with a consistent level of surgical expertise and technique. All patients will undergo minimally invasive procedures adhering to the principles of TME. The surgical process begins with a comprehensive examination of the abdominal cavity, followed by a precise dissection along the plane separating the mesorectum from the parietal fascia, with a focus on preserving the autonomic

nerves. Apical lymph nodes will be excised regardless of whether the inferior mesenteric artery is ligated high or low. In cases of high ligation, the inferior mesenteric artery will be identified and secured 2 cm from its origin. For low ligation, the left colic artery will be identified and spared, with the inferior mesenteric artery being ligated just below the left colic artery's origin. The inferior mesenteric vein will be tied off and cut either at the lower edge of the pancreas or at a comparable level for low artery ligation, depending on the surgeon's preference. To ensure adequate bowel length for an anastomosis or stoma where tension is anticipated, further colon or splenic flexure mobilization will be undertaken. A diverting ileostomy will be performed in selected patients at the discretion of the surgeon.

Detection of CTCs

Peripheral venous blood (5 ml) was collected from the same site at two specific time points for each patient: first, after the induction of anesthesia but prior to the commencement of surgery, and second, immediately after the closure of all abdominal wall incisions. The actual testing volume was 3 ml. All CTCs were analyzed and quantified using the FR+CTCs detection kit (Geno Biotechn Co Ltd), certified by the China Food and Drug Administration. The process of CTC enrichment began with the lysis of erythrocytes, followed by the separation of leukocytes from whole blood using immunomagnetic techniques. Subsequently, the FR+CTC concentration in each sample was determined through ligand-targeted polymerase chain reaction (PCR). The self-referencing

CTC unit (notated as FU), derived from a standard curve, was employed to measure the concentration of FR+CTC in 5 ml of peripheral blood. This quantification involved the use of a range of standards with oligonucleotides varying from 10^{-14} to 10^{-9} M, equivalent to 2 to 2×10^5 CTC units per 3 ml of blood. This procedure was also reported in a previous study [17].

Statistical Analysis

Statistical analysis was performed using R (Version 4.4.2; <http://www.Rproject.org/>) and SPSS 19.0 (SPSS®, Chicago, IL, USA). Continuous data will be presented as means with standard deviation (SD). Categorical data will be presented as numbers and percentages. The t test or Wilcoxon rank sum test will be used to compare continuous data, and chi-square analysis or Fisher's exact test will be used to compare categorical variables. The plot of patient CTC values was constructed by the packages of "ggplot2", "reshape2", and "dplyr" (<http://CRAN.Rproject.org/packages>) in R. A two-tailed $p < 0.05$ is considered statistically significant.

Results

A total of 29 patients were included in the study, with 15 in the A-first group and 14 in the V-first group. The clinicopathological characteristics are shown in Table 1, surgery-related outcomes and postoperative complications are shown in Table 2. The preoperative and postoperative CTC values of each patients are shown in Fig. 2.

Demographics and clinicopathological characteristics

The demographic and clinicopathological characteristics such as age, sex, ASA score, CEA level, tumor size, and pathologic staging showed no significant differences between the two groups (all $p > 0.05$, Table 1).

Surgery-related outcomes and postoperative complications

The primary surgical outcomes, including the duration of the surgery, the volume of blood loss, lymph nodes harvested, apical lymph nodes harvested and postoperative complications did not differ significantly between the groups (all $p > 0.05$, Table 2). Two patients in V-first group experienced postoperative complications: one had an infection at the perineal incision following abdominoperineal resection, while the other had bleeding at the anastomotic site. Both were classified as Grade II according to the Clavien-Dindo classification. No intraoperative complications occurred in both groups.

Preoperative and postoperative CTC values

As shown in Fig. 2, compared to preoperative CTC levels, 3 (3/15, 20%) patients in the A-first group showed a decrease in CTCs postoperatively, and 5 (5/14, 36%)

patients in the V-first group showed a decrease in CTCs postoperatively.

Discussion

Multiple studies have demonstrated that CTCs in peripheral blood can be used as potential indicators for predicting postoperative recurrence and prognosis in colorectal cancer patients [11, 12]. Theoretically, ligating the vein first might help reduce the backflow or spillage of tumor cells into the systemic circulation, potentially lowering the risk of metastatic spread. The present study aimed to investigate the impact of the ligation sequence of the inferior mesenteric artery and vein on the dissemination of CTCs in laparoscopic rectal cancer surgery. In our cohort, 36% of patients in the V-first group exhibited a reduction in CTCs postoperatively, compared to 20% in the A-first group. This preliminary observation suggests that the sequence of vascular ligation could potentially influence the dynamics of tumor cell dissemination during surgery. This has prompted us to conduct a larger-sample prospective, randomized controlled study to confirm this hypothesis.

In this study, there were no significant differences between the two groups in terms of surgical duration, blood loss, number of lymph nodes harvested, or postoperative complications. Notably, while different sequences of vascular ligation might most likely affect the number of apical lymph nodes harvested, there was no significant difference between the groups in this respect either. Although two patients in the V-first group experienced postoperative complications. One with bleeding at the anastomotic site and the other with an infection at the perineal incision, these complications are unlikely to be related to vascular ligation. Overall, there were no significant differences in the incidence of postoperative complications between the two groups. This demonstrates that different sequences of vascular ligation are technically mature for experienced teams, establishing a safe and feasible foundation for advancing to further research.

In the present study, we utilized the FR+CTCs detection kit (Geno Biotechn Co Ltd), certified by the China Food and Drug Administration, to measure CTC levels. Considering the inherent variability in FR+CTC measurements, a 15% cut-off was established to minimize the impact of physiological and detection factors on CTC changes. This threshold helps reduce the likelihood of false positives, ensuring that the observed changes more accurately reflect true surgical effects rather than those induced by physiological or detection factors.

Given the absence of prior literature on the impact of vascular ligation sequence on the prognosis of rectal cancer patients, the current study served as a pilot investigation aimed at exploring the safety, feasibility, and effects on peripheral blood CTC levels of different vascular

Table 1 The comparison of clinicopathological characteristics between the A-first and V-first groups

Clinicopathologic characteristics	A-first n = 15	V-first n = 14	P†
Sex			0.356
Male	9 (60.0)	6 (42.9)	
Female	6 (40.0)	8 (57.1)	
Age (year)*	62.6 (8.1)	61.3 (7.1)	0.647‡
ASA score			0.292
1	15 (100.0)	13 (92.9)	
2	0	1 (7.1)	
BMI (kg/m ²) *	39.1 (6.6)	36.8 (4.3)	0.313‡
CEA level (ng/ml) *	6.9 (7.0)	4.5 (5.2)	0.297‡
Surgery type			0.372
Low anterior resection	8 (53.3)	8 (57.1)	
Low anterior resection + diverting ileostomy	5 (33.3)	2 (14.3)	
Low anterior resection + diverting ileostomy + partial hepatectomy [#]	1 (6.7)	0	
Low anterior resection + bilateral salpingo-oophorectomy [¶]	0	1 (7.1)	
Abdominoperineal resection	1 (6.7)	3 (21.4)	
Preservation of the left colic artery			0.474
Yes	5 (33.3)	3 (21.4)	
No	10 (66.7)	11 (78.6)	
Tumor size*	3.6 (1.2)	3.2 (1.1)	0.414‡
Pathologic tumor category			0.489
T1	3 (20.0)	2 (14.3)	
T2	3 (20.0)	2 (14.3)	
T3	9 (60.0)	8 (57.1)	
T4a	0	2 (14.3)	
Pathologic node category			0.196
N0	11 (73.3)	7 (50.0)	
N1	4 (26.7)	7 (50.0)	
AJCC 8th staging			0.645
I	5 (33.3)	4 (28.6)	
II	6 (40.0)	4 (28.6)	
III	4 (26.7)	6 (42.9)	
Perineural invasion			0.599
No	11 (73.3)	9 (64.3)	
Yes	4 (26.7)	5 (35.7)	
Lympho-vascular invasion			0.184
No	12 (80.0)	8 (57.1)	
Yes	3 (20.0)	6 (42.9)	
Tumor differentiation			0.849
Well-moderate	6 (40.0)	7 (50.0)	
Moderate	8 (53.3)	6 (42.9)	
Moderate-poor	1 (6.7)	1 (7.1)	
MMR status			0.292
pMMR	15 (100.0)	13 (92.9)	
Not reported	0	1 (7.1)	
Adjuvant chemotherapy			0.356
No	9 (60.0)	6 (42.9)	
Yes	6 (40.0)	8 (57.1)	
Adjuvant radiotherapy			0.782
No	10 (66.7)	10 (71.4)	
Yes	5 (33.3)	4 (28.6)	

Values in parentheses are percentages unless indicated otherwise; *values are mean (standard deviation). † χ^2 or Fisher's exact test, except ‡Student's t test. V-first: vein-first; A-first: artery-first; ASA, American Society of Anesthesiology; BMI, body-mass index; AJCC, American Joint Committee on Cancer

[#] The patient underwent partial hepatectomy because a gray-white nodule measuring about 0.5 cm was observed at the junction of liver segments IV and V during the operation. Both the intraoperative frozen section and the postoperative pathology indicated a bile duct adenoma

[¶] The patient underwent bilateral salpingo-oophorectomy because during the operation, large cysts were observed on both ovaries, with the right side measuring about 10 cm and the left side about 8 cm. Postoperative pathology indicated ovarian cysts

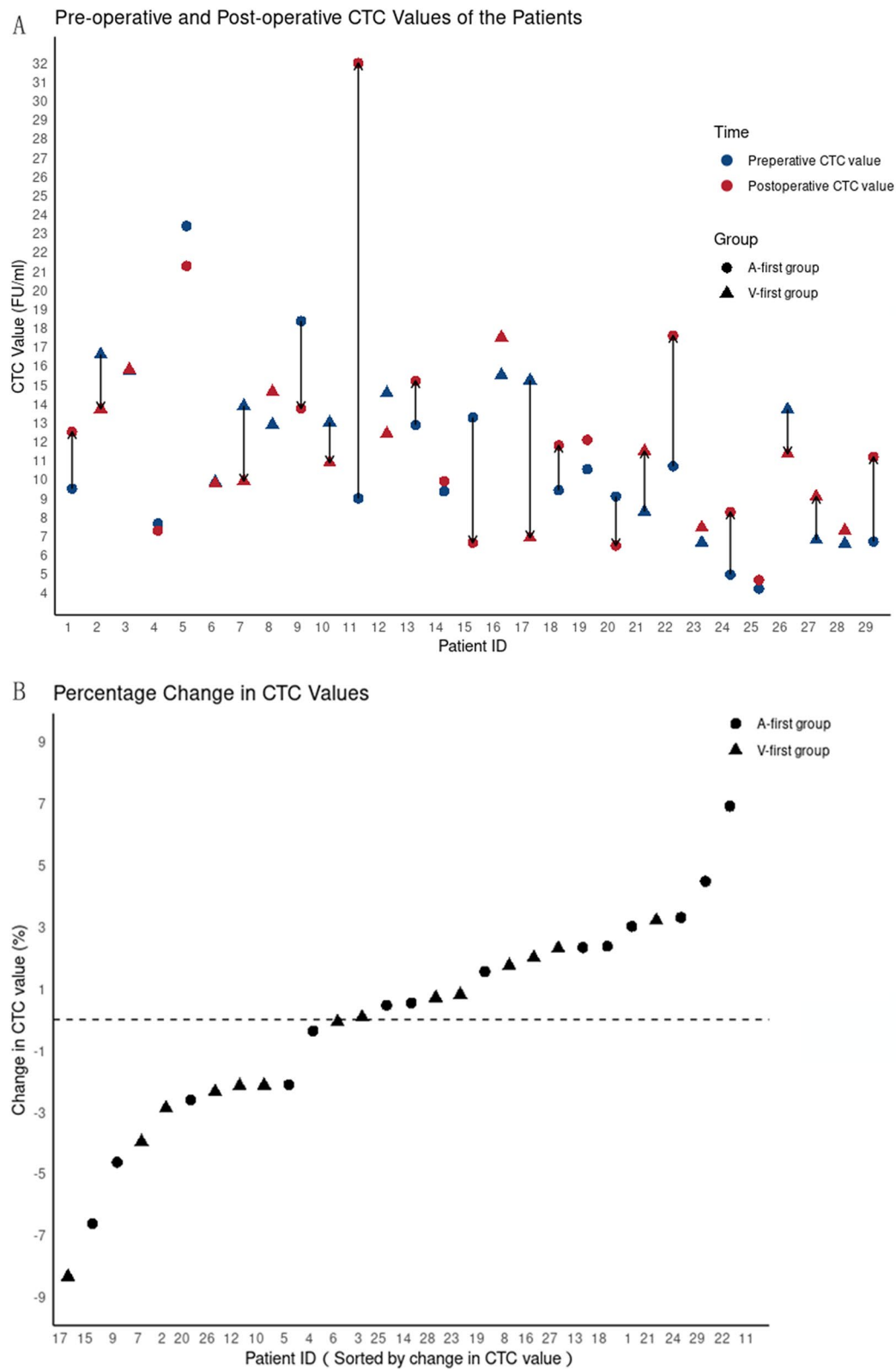


Fig. 2 Preoperative and postoperative CTC values for the 29 patients. **A:** Blue dots represent pre-operative CTC values, and red dots represents post-operative CTC values. An arrow symbol indicates significant differences (with a difference $\geq 15.0\%$) between the two CTC measurements for a patient, with the arrow pointing from preoperative to postoperative. **B:** The dots represent the percentage change in CTC values before and after surgery. V-first: vein-first; A-first: artery-first; CTC: circulating tumor cell

Table 2 The comparison of surgery-related outcomes and postoperative complications between the A-first and V-first groups

Clinicopathologic characteristics	A-first n = 15	V-first n = 14	P†
Surgical duration (min)*	200.7 (36.9)	169.6 (50.3)	0.068‡
Blood loss (ml)*	58.7 (32.0)	49.3 (18.2)	0.346‡
Lymph nodes harvested*	20.1 (4.8)	18.2 (5.9)	0.346‡
Apical Lymph nodes harvested*	2.1 (1.9)	2.4 (2.3)	0.654‡
Postoperative complication			0.129
No	15 (100.0)	12 (85.7)	
Yes	0	2 (14.3)‡	

Values in parentheses are percentages unless indicated otherwise; *values are median (interquartile range). † χ^2 or Fisher's exact test, except ‡ Student's t test. V-first: vein-first; A-first: artery-first

‡ Two patients experienced postoperative complications; one had an infection at the perineal incision after undergoing an abdominoperineal resection, and the other had bleeding at the anastomotic site. Both were classified as Grade II according to the Clavien-Dindo classification

ligation sequences. However, it has its limitations. Firstly, the small sample size may reduce the statistical power of the findings. Secondly, the observational nature of CTC measurements without a randomized design specifically for this endpoint limits our ability to conclusively determine the impact of ligation sequence on CTC dynamics. To address these issues, we have designed a larger, prospective, randomized trial to robustly assess how these surgical techniques might influence CTC levels and long-term oncological outcomes, such as disease-free survival and overall survival. This upcoming study has been registered on ClinicalTrials.gov under the identifier NCT05807646.

In conclusion, our study indicates that both A-first and V-first ligation sequences are viable and safe options in laparoscopic rectal cancer surgery. The V-first approach may be more effective in reducing levels of CTCs in peripheral blood. Further randomized studies are warranted to explore these findings comprehensively.

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Author contributions

PT, NCB, HH, and LC have made substantial contributions to the conception and design of the study. PT and HH have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published.

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Data availability

The datasets generated during the current study will be available from the corresponding author on reasonable request after the publication of the main findings.

Declarations

Ethics approval and consent to participate

This study received ethical approval from Sichuan Cancer Hospital Ethics Committee (SCCHEC-02-2024-102). All patients provided informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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