

Lymphadenectomy Around Inferior Mesenteric Artery in Low-Tie vs High-Tie Laparoscopic Anterior Resection: Short- and Long-Term Outcome of a Cohort of 614 Rectal Cancers

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Background: Preservation of the left colic artery in low-tie (LT) of inferior mesenteric artery remains controversial compared to high-tie (HT) in the colon and rectal cancers, for lymph node dissection, anastomotic leakage, and oncological outcome. This cohort study aims to analyze short- and long-term outcomes of laparoscopic anterior resections in LT vs HT for rectal cancers.

Methods: We analyzed a cohort of laparoscopic AR for RC from 2013 to 2016 at Renji Hospital, Shanghai, China. Short- and long-term outcome in LT vs HT group were compared for clinico-demographic characteristics, operative-time, lymph node dissection, short-term 30-day outcome, and long-term 3- and 5-year overall survival as well as disease-free survival. The χ^2 , *t*-test, and logistic regressions analysis were used and $p < 0.05$ was considered significant.

Results: The cohort consisted of 614 laparoscopic AR with LT (236) and HT (378). The clinicodemographic characteristics were comparable among the groups. The surgery took longer in LT. The yield of LND was similar. Leakage occurred in 12.21% (n=75). Leakage was fewer in LT than HT, 8.89% vs 14.28%, $p = 0.047$. The postoperative severe complications were higher in HT. The 30-day mortality was nil. The long-term 3- and 5-year overall survival and disease-free survival were similar in LT and HT.

Conclusion: The LT with preservation of left colic artery had similar lymph node yield, but lower leakage and complications than HT in laparoscopic anterior resections for rectal cancers. The long-term 3- and 5-year overall and disease-free survival were similar in the two groups.

Keywords: anastomotic leakage, Clavien-Dindo complications, laparoscopic anterior resection, left colic artery, low-tie high-tie of the inferior mesenteric artery, rectal cancer

Plain Language Summary

Our findings in a cohort of 641 patients with rectal cancer who underwent laparoscopic anterior resection affirm that low-tie (LT) of the inferior mesenteric artery with preservation of left colic artery maintains the oncological principle for lymph node harvesting including at the root of the inferior mesenteric artery. The LT group had fewer anastomotic leakage compared to high-tie (HT), and comparable 3- and 5-year long-term outcomes of overall survival and disease-free survival.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and is of concern in China due to its steady increase in age-standardized incidence rates

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(ASIR) from 14.25 to 25.27 per 100,000 observed during 1990–2016, with an average annual percentage change of 2.34, and Shanghai at 2nd position with an ASIR of 32.30 after Hong Kong at 39.97.¹

Total mesorectal excision (TME) is the gold standard for rectal cancer (RC),² but the controversies continue for high-tie (HT) with ligation of the inferior mesenteric artery (IMA) at its root above the branching of left colic artery “LCA” vs low-tie (LT) with ligation of IMA below LCA. The HT is credited for ease of lymph node dissection (LND) around IMA for staging and oncological outcome plus tension-free anastomosis of the remaining colon.^{3,4} The compromise of blood supply leading to colon ischemia,⁵ hypoperfusion and anastomotic leakage (AL),^{6,7} damage to superior hypogastric plexus,⁸ and genitourinary defecatory functions⁹ are some concerns for the HT. The LT has shown a decrease in leakage with the comparable oncological outcome and 5-year long-term survival.^{8,10} Chinese studies advocate preoperative 3D CT reconstruction to recognize variations¹¹ in the mesenteric artery and vein to preserve LCA and expertise in laparoscopic¹² procedure.

In this large cohort of laparoscopic anterior resection for rectal cancer, we aim to analyze the feasibility, safety, and oncological outcome of low-tie vs high-tie.

Methods

This retrospective cohort study included patients with rectal cancer who underwent laparoscopic anterior resection from January 2013 to December 2016 at the Department of Gastrointestinal Surgery, Renji Hospital, Jiao Tong University School of Medicine, Shanghai, China. Patients with a metastatic disease requiring additional procedures (organ resection), documented ischemic/atherosclerosis vascular disease, open surgery, abdominoperineal resection, having diverting stomas, and Hartmann’s procedures were excluded. The data from this cohort of AR for RC were analyzed and compared between LT vs HT groups for clinicodemographic variables (age, gender, body mass index “BMI”, diabetes, hypertension, neoadjuvant therapy, American Society of Anesthesiologist ASA grade, tumor size and location in the upper or lower rectum, and carcinoembryonic antigen CEA values). The operative data analyzed included duration of surgery (time for IMA ligation and completion of TME), blood loss, blood transfusion, level of colorectal anastomosis from the anal verge, the yield of LND around IMA, and total LN, tumor margins, and histopathology findings. Post-operative 30-day

short-term outcome included urinary retention, ileus, flatus, AL, surgical site infection (SSI), grade of complication as per Clavien-Dindo (CD) classification¹⁵, hospital stay, and mortality. The long-term outcome included 3- and 5-years overall survival (OS) and disease-free survival (DFS). Ethical approval was obtained by the Institute Research Ethics Committee of Renji Hospital. Patient consent was not required because it was already archived data in the hospital electronic database, and we anonymized it for personal identification during analysis in compliance with the Declaration of Helsinki.

Data are from Renji Hospital. All laparoscopic surgeons are specialists with experience of more than 10 years of service at Renji. As per the hospital practice, a medial-to-lateral approach for laparoscopic dissection was used.¹³ In HT, the IMA was ligated at its origin within 1 cm from the aorta proximal to the branching of LCA. In LT, the IMA was skeletonized, and en-bloc LN dissection continued medially along with the IMA up to its root at the abdominal aortic (AA) plane and IMA was clipped distal to the branching of LCA to preserve the LCA,¹⁴ Figure 1A–B. The proximal colon was divided at 10 cm from the lesion. The distal rectal margin was maintained at 3 cm for tumors in the proximal rectum above the peritoneal reflection and 2 cm for tumors in the distal rectum below the peritoneal reflection. The specimen was removed via a small abdominal wall incision. The double staple technique was used for end-to-end colorectal anastomosis. An air leak test was performed to ensure the integrity of anastomosis, Figure 2A–D. The follow-up after discharge included clinical physical examination at 4–6 weeks and laboratory biochemical and radiological assessments every 3 months during the first 2-year, and thereafter every 6 months up to 5 years, as per our hospital protocol.

In this study, the short-term outcome was defined as complications (including bleeding, AL, colon ischemia, peritonitis, infection, urinary retention, ileus, or death) and their management (medical, radiological, surgical) within 30 postoperative days. The postoperative hospital stay was measured from the date of surgery to the date of discharge. Anastomotic leakage was analyzed as “leakage or no leakage” mentioned in the discharged diagnosis of the electronic database. In our hospital, the clinicians follow the diagnosis of leakage as defined by the International Study Group of rectal cancer.¹⁶ Follow-up information was obtained from medical records, outpatient clinic (and/or through phone interview) including recurrence of cancer, site of recurrence, and death until

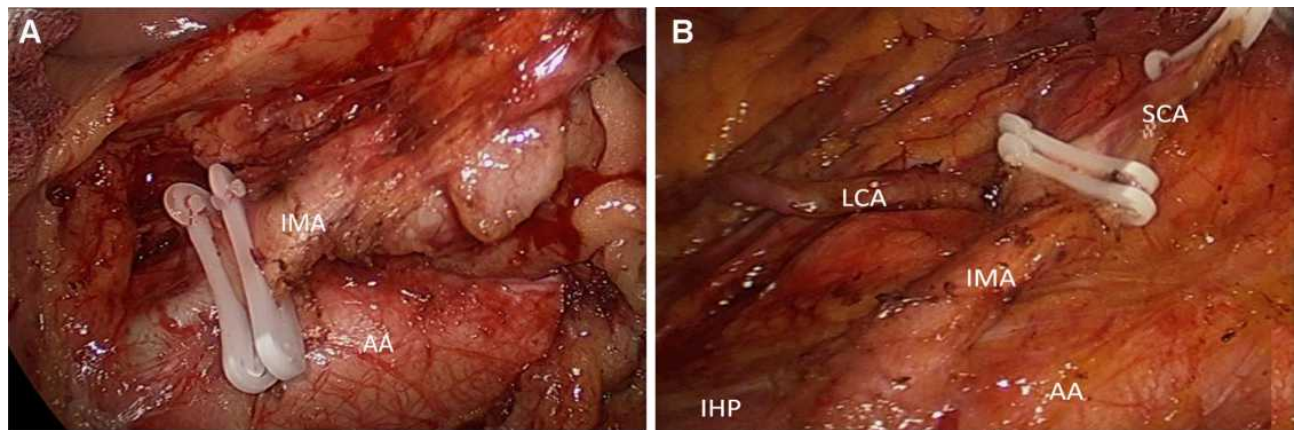


Figure 1 (A) High-tie, the IMA is ligated at its origin within 1 cm from the aorta, with dissection of the apical lymph nodes (LN); (B) Low-tie, the IMA and the proximal left colic artery (LCA) are skeletonized, LCA is preserved, the superior rectal artery (SRA) is ligated, LN dissection medially along the IMA root, including the abdominal aortic (AA) plane.

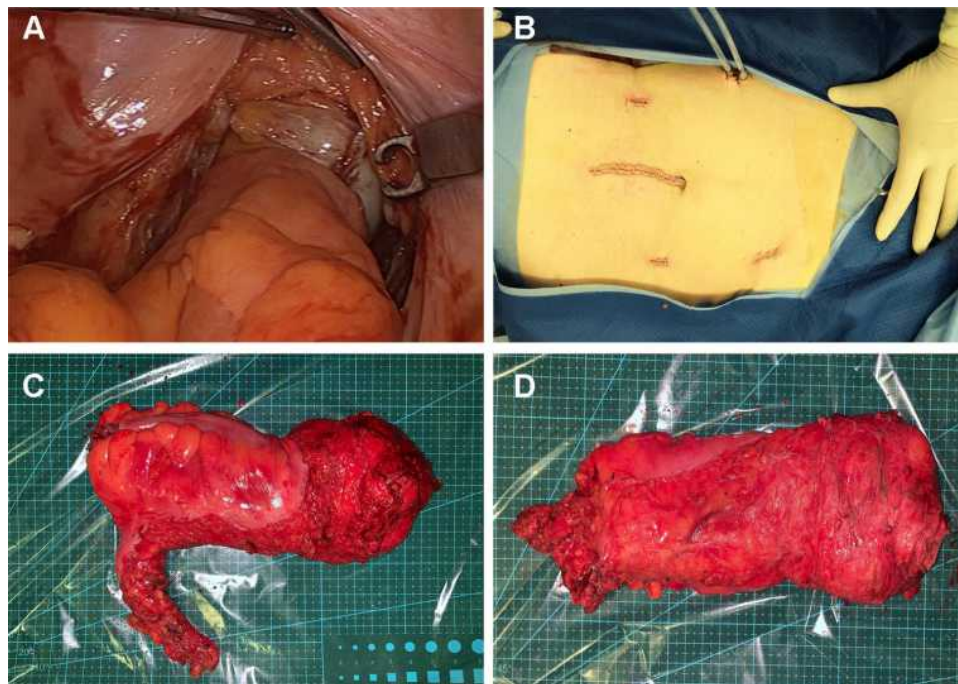


Figure 2 (A) Tension-free anastomosis after low-tie of IMA and preservation of LCA; (B) Completion of laparoscopic surgery for rectal cancer and skin closure of ports; (C-D) Retrieved specimen after low-tie and total mesorectal excision (TME) for rectal cancer.

December 2019. Long-term outcome was defined as OS and DFS in 3 and 5 years.

We described the baseline characteristics, tumor characteristics, and oncologic treatments using descriptive statistics and compared these variables between high-tie and low-tie groups using the χ^2 test for categorical variables and Wilcoxon Signed Rank Test for continuous variables. The categorical variables are expressed as frequency (%) and continuous variables as the median. Univariate and

multivariate logistic regression was performed to identify the risk factors for anastomotic leakage (AL) in rectal tumor patients. We used univariable logistic regression for the association of level of ligation (high or low) with outcome in individual models including age ≥ 65 years, male, diabetes and/or hypertension, neoadjuvant treatment, and tumor location in the lower rectum. For long-term outcomes, Kaplan–Meier curves were plotted and patients with and without low-tie were compared using the Log

rank test. Cox regression analyses were used to investigate the influence of low-tie on overall survival and disease-free survival. Missing values were disregarded and thus not imputed. Exposure and outcome variables were complete for all individuals. All baseline, tumor-related, and cancer treatment-related variables were complete for all individuals. We conducted the statistical analysis in SPSS 22.0 (IBM Corporation, 2013, New York, USA) and R project version 3.3.2 (Foundation for Statistical Computing, Vienna, Austria). We considered a two-tailed p-value of < 0.05 to be statistically significant.

Results

Overall, a cohort of 614 (LT 236, HT 378) patients were included in the study. In the LT group, the LCA was preserved in all cases, and the division of LCA was not required due to tension at the colorectal anastomosis. In demographic characteristics, diabetes and/or hypertension in the LT group were more common compared to HT, 19.07 vs 12.69, $p=0.032$. Neoadjuvant treatment was performed in 47 (12.54%) patients, similar in both groups, 11.38% in HT and 14.41% LT, $p=0.270$. Tumor located in lower rectum was 238 (38.76%), more in LT (39.83%) than HT (32.76%), $p=0.080$, [Table 1](#).

In perioperative parameters, the duration of surgery in LT (146.0 ± 2.46 min) was longer than in HT (138.6 ± 2.01 min), $p=0.021$. The time required for IMA tie in LT (41.46 ± 0.66 min) was longer than HT (32.69 ± 0.59 min), $p=0.000$. Blood loss, LND, level of anastomosis from the anal verge, and pathological margins were not significantly different in the two groups. Patients with positive IMA root nodes also had positive intermediate or perirectal lymph nodes, [Table 2](#).

In postoperative outcome, 207 (33.71%) patients had complications, 30.08% in LT vs 35.98% in HT, $p=0.133$. Postoperative severe complications (CD grade III–IV) were lower in LT than HT (7.98% vs 11.90%, $p=0.120$).

Anastomotic leaks were found in 75 (12.21%) patients, less in LT (8.89%) than HT (14.28%), $p=0.047$. Hazard ratio, uni- and multivariate analysis for factors associated with anastomotic leakage included male, elder age, diabetes and/or hypertension, neoadjuvant treatment, and lower rectum. As per our main focus, we estimated the effect of low-tie in anastomotic leakage and found that for tumors located in the lower rectum, there was fewer leakage in LT than HT (10.64% vs 20.83%), $p=0.040$. Patients with associated comorbidities

Table 1 Clinicodemographic Profile of Patients with Low-Tie vs High-Tie of the Inferior Mesenteric Artery in Laparoscopic Anterior Resection of Rectal Cancer, N=614

Clinical Profile	LT ^a 236 (38.44%)	HT ^b 378 (61.56%)	p-value
Age (years)	62.05 ± 0.68	63.25 ± 0.58	0.189
BMI	22.12 ± 0.18	22.34 ± 0.15	0.372
Gender			0.784
Male	140 (59.32)	220 (58.20)	
Female	96 (40.68)	158 (41.80)	
Diabetes and/or hypertension			0.032
Yes	45 (19.07)	48 (12.69)	
No	191 (80.93)	330 (87.31)	
Neoadjuvant			0.270
Yes	34 (14.41)	43 (11.38)	
No	202 (85.59)	335 (88.62)	
ASA grade			0.547
1	126 (53.40)	189 (50.00)	
2	58 (24.58)	108 (28.57)	
3	52 (22.02)	81 (21.43)	
Tumor size (cm)			0.181
≤ 5	152 (64.41)	223 (58.99)	
> 5	84 (35.59)	155 (41.01)	
CEA level (ng/mL)			0.979
≤ 5	127 (53.81)	203 (53.70)	
> 5	109 (46.19)	175 (46.30)	
Tumor location			0.080
Upper rectum ^c	142 (60.17)	234 (67.24)	
Lower rectum ^c	94 (39.83)	144 (32.76)	

Notes: ^aLT- low-tie with ligation of inferior mesenteric artery (IMA) distal to the branching of the left colic artery (LCA) with en-bloc lymph node dissection around IMA and preservation of LCA, ^bHT- high-tie with ligation of IMA at its root proximal to the branching of LCA; ^cTumor in upper rectum – above the peritoneal reflection and lower rectum below the peritoneal reflection.

Abbreviations: ASA, American Society of Anesthesiologist; CEA, carcinoembryonic antigen.

of diabetes and/or hypertension, with neoadjuvant treatment, age ≥ 65 years, and male gender also had a lower leak in LT than HT, but the difference was not significant, $p>0.05$, [Tables 3 and 4](#).

In short-term outcome, there was no death within 30 days in either group. Long-term outcomes in two groups were not significantly different, with 3-years OS (LT 81.78% vs HT 83.33%, $p=0.658$) and DFS (LT 78.38% vs HT 83.33%, $p=0.143$) and 5-years OS (LT 59.51% vs HT 61.46%, $p=0.671$) and DFS (LT 52.20% vs 53.52%, $p=0.690$), [Table 5](#), [Figure 3A–D](#).

Table 2 Operative Findings of Rectal Cancer Patients with LT vs HT in Laparoscopic Anterior Resection of Rectal Cancer, N=614

Clinicopathological Feature	LT 236 (38.44%)	HT 378 (61.56%)	p-value
Duration of surgery (min)	146.0 ± 2.46	138.6 ± 2.01	0.021
Time for IMA tie	41.46 ± 0.66	32.69 ± 0.59	0.000
Time for TME	74.79 ± 2.13	73.46 ± 2.14	0.675
Blood loss (mL)	125.1 ± 5.74	113.6 ± 4.03	0.092
Blood transfusion (n)	9 (3.81)	11 (2.91)	
Anastomosis from anal verge (cm)	4.02 ± 0.15	3.93 ± 0.15	0.693
No. of lymph nodes harvested			
Total	17.23 ± 0.30	17.51 ± 0.22	0.452
Lymph nodes around IMA	3.15 ± 0.06	3.23 ± 0.05	0.338
Intermediate lymph nodes	3.88 ± 0.09	3.72 ± 0.06	0.116
Perirectal lymph nodes	10.20 ± 0.30	10.56 ± 0.22	0.331
Lymph node involvement			
Lymph nodes around IMA	13 (5.5)	17 (4.49)	
Intermediate lymph nodes	21 (8.89)	37 (9.78)	
Perirectal lymph nodes	87 (36.86)	134 (35.45)	
Pathological proximal margin (cm)	13.90 ± 0.09	14.04 ± 0.08	0.249
Pathological distal margin (cm)	2.87 ± 0.08	2.79 ± 0.06	0.444

Table 3 Risk Factors for Anastomotic Leakage in Patients with LT vs HT in Laparoscopic Anterior Resection for Rectal Cancer, N=614

Clinicopathological Feature	LT N (%)	HT N (%)	p value
Age ≥ 65 years	105	194	
AL	13 (12.38)	37 (19.02)	0.148
No-AL	92 (87.62)	157 (80.98)	
Male	140	220	
AL	15 (10.71)	21 (12.27)	0.653
No-AL	125 (89.29)	199 (87.73)	
Diabetes and/or hypertension	45	48	
AL	5 (11.11)	11 (22.91)	0.132
No-AL	40 (88.89)	37 (77.09)	
Neoadjuvant treatment	34	43	
AL	5 (14.71)	10 (23.26)	0.347
No-AL	29 (85.29)	33 (76.74)	
Tumor location in lower rectum	94	144	
AL	10 (10.64)	30 (20.83)	0.040
No-AL	84 (89.36)	114 (79.17)	

Discussion

Our finding shows that the most feared complications in colorectal surgery, the leakage occurred in 75 (12.21%), and at a significantly lower rate in the LT group

compared to HT, 8.89% vs 14.28%, $p=0.047$. Among the associated risk factors, only the level of “tumor in lower rectum” was significantly associated with leakage, occurring in 10 (10.64%) in LT compared to 30 (20.83%) in HT group, $p=0.040$. This could be due to better blood supply in the LT group by the preservation of LCA. Other studies have reported that male gender, elder age, diabetes and/or hypertension, neoadjuvant treatment, and tumor in the lower rectum were associated with anastomotic leakage.^{17–19} In our study, “diabetes and/or hypertension, neoadjuvant treatment, age ≥ 65 years, and male gender” had a higher percentage of leakage in HT than LT, but the difference was not statistically significant.

We found no significant difference in yield of lymph node between the two groups, both in terms of the number of nodes harvested around IMA (LT 3.15 ± 0.06 vs HT 3.23 ± 0.05 , $p=0.338$) and total lymph nodes (LT 17.23 ± 0.30 vs HT 17.51 ± 0.22 , $p=0.452$). For the past 100 years, it is still a controversial topic, and debate for the optimal level of IMA ligation has continued for better radical resection and oncological staging.^{20,21} Our results for this cohort of 614 rectal cancer suggest LT maintains the oncological principle of radicality with adequate LND around IMA in laparoscopic anterior resection.

Table 4 Hazard Ratio in for Anastomotic Leakage in Patients with LT vs HT in Laparoscopic Anterior Resection for Rectal Cancer, N=614

Clinical Parameter	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
IMA ligation (high-tie vs low-tie)	1.62	1.56–1.65	0.047	1.71	0.99–2.94	0.051
Age (≥65 vs <65 years)	1.49	1.45–1.53	0.001	2.15	1.29–3.58	0.003
Gender (male vs female)	1.59	1.55–1.63	0.031	1.55	0.95–2.55	0.078
Tumor Size (>5 cm vs ≤5 cm)	1.30	1.27–1.34	0.421	-	-	-
Diabetes and/or hypertension (Yes vs No)	1.15	1.12–1.18	0.868	-	-	-
Tumor location (low vs high)	1.39	1.35–1.43	0.011	1.66	0.98–2.82	0.058
Neoadjuvant treatment (Yes vs No)	1.13	1.10–1.15	0.043	1.54	0.77–3.06	0.216

Abbreviations: HR, hazard ratio; CI, confidence interval; p, p value.

Table 5 Long-Term Results of Overall Survival (OS) and Disease-Free Survival (DFS) in Patients with LT vs HT Anterior Resection of Rectal Cancer, N=614

Long-Term Outcome	LT %	HT %	p-value
3-year OS rate (%)			
All patients (n=614)	81.78	83.33	0.658
With LN metastasis around IMA	69.23	76.47	0.726
Without LN metastasis around IMA	84.30	86.15	0.543
3-year DFS rate (%)			
All patients (n=614)	78.38	83.33	0.143
With LN metastasis around IMA	61.53	64.71	0.951
Without LN metastasis around IMA	79.37	84.21	0.148
5-year OS rate (%)			
All patients (n=532)	59.51	61.46	0.671
With LN metastasis around IMA	53.85	53.33	0.924
Without LN metastasis around IMA	59.90	61.86	0.667
5-year DFS rate (%)			
All patients (n=532)	52.20	53.52	0.690
With LN metastasis around IMA	38.46	40.00	0.968
Without LN metastasis around IMA	53.13	54.17	0.723

In the present study, the overall postoperative early recovery in terms of ‘time to first flatus’ was better in LT. We also found that there were fewer complications of mild grade (CD I–II) and severe grade (CD III–IV) in LT than HT. However, the differences were statistically not significant. The dreaded short-term complication of leakage was significantly less in LT than in HT. However, we could analyze “leakage or no leakage” as per the discharge diagnosis in the electronic record, and could not further analyze the grading of the anastomotic leak as defined by the International Study Group of rectal cancer.¹⁶ However, in our hospital, the clinicians follow the diagnosis of leakage as per international

norms. Studies have shown that patients with leakage have a poor perioperative recovery, requiring a longer period of antibiotics, drainage of collection, and reoperation and may cause local recurrence and diminished survival.^{22,23}

Maintaining blood supply and ensuring a tension-free anastomosis reduces the incidence of AL.²⁴ Preserving LCA in LT ensures adequate blood supply and oxygenation to the remaining colon. In contrast, the blood supply of the remaining distal colon in the case of HT solely depends on the middle colic and marginal arteries.^{25,26} The doppler flowmetry has shown IMA clamping results in a >50% reduction in blood flow²⁷ to the anastomosis and development of proximal bowel necrosis or ischemia^{5,28} after HT of IMA.

Similar to our finding of reduced rate of AL in LT, other studies have also reported a reduced rate of leakage in LT.²⁹ However, there are reports which did not demonstrate a statistical difference in leakage between LT and HT.^{30,31} This may be due to other related factors related to surgeons and/or patients which may have a role in leakage of the anastomosis.

Tension at anastomosis is an important factor for leakage. The HT has traditionally been thought to help preserve sufficient bowel length for tension-free anastomosis.^{4,32} However, reports show that preserving LCA and mobilization of splenic flexure provide adequate bowel length for tension-free anastomosis.²⁹ In the present study, our results show that tension-free anastomosis is feasible in all cases in the LT group, without the need for re-do of anastomosis because of the in-adequate remaining length of the colon or undue tension for anastomotic reconstruction. And, significantly less leakage was observed in our cohort of patients with adequate length of the remaining colon for tension-free anastomosis was reflected in the LT group.

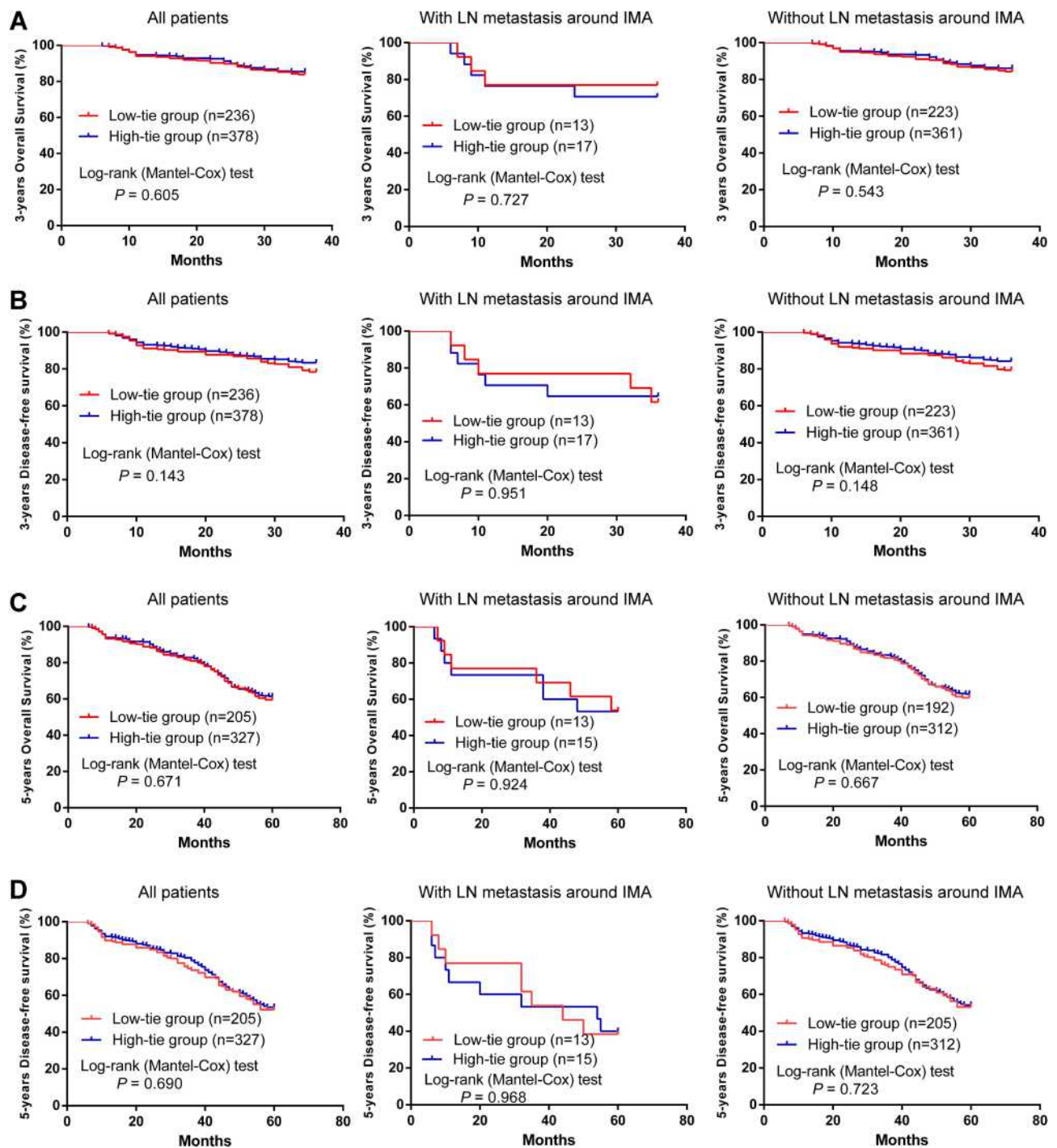


Figure 3 Long-term outcomes in the low-tie groups and high-tie groups. **(A)** 3-years OS with all patients, LN metastasis around IMA patients, and without LN metastasis around IMA patients; **(B)** 3-years DFS with all patients, LN metastasis around IMA patients, and without LN metastasis around IMA patients; **(C)** 5-years OS with all patients, LN metastasis around IMA patients, and without LN metastasis around IMA patients; **(D)** 5-years DFS with all patients, LN metastasis around IMA patients, and without LN metastasis around IMA patients.

Historically, the HT of IMA in CRC has been credited for the ease of LND, including the LN at IMA root, to achieve accurate pathological staging and improvement in overall prognosis.^{32,33} The IMA root lymph nodes metastasis has been reported in 1.7 to 7.8% of cases.^{34,35} The

development of laparoscopic technology and the feasibility of LND around IMA with preservation of LCA is a feasible and valid surgical treatment. In a randomized clinical trial of 324 RCs, the 5-year outcome of the LT group did not differ from the HT.³⁶ Our study has

reaffirmed the good oncological outcomes of LT with no significant differences between the number of harvested lymph nodes compared to HT (17.23 ± 0.30 vs 17.51 ± 0.22). Also, we found that the long-term 3- and 5-year survival (OS and DFS) of LT and HT were comparable.

Some of the limitations of the present study include those inherent to the retrospective data analysis. There may be a selection bias from the individual surgeon for techniques and we could not analyze the variables like metastasis, atherosclerosis, use of neoadjuvant therapy, transanal drainage tube, diverting stoma, circumferential resection margin, the severity of leak due to inconsistency in detail in the electronic database. However, clinicians at our hospital do practice as per international norms to define anastomotic leakage, the preoperative staging of the tumor and neoadjuvant therapy, etc. All these issues may be answered by a prospective study with detailed data-keeping, preferably a multi-institutional accumulation of data in Shanghai and at the national level. In the present study, our main aim was to analyze the feasibility, safety, and oncological outcome of low vs high ligation of the inferior mesenteric artery.

In conclusion, our findings of a retrospective analysis of a cohort of 641 patients with rectal cancer who underwent laparoscopic anterior resection affirm that low-tie (LT) of the inferior mesenteric artery with preservation of left colic artery maintains the oncological principle for lymph node dissection around and at the root of the inferior mesenteric artery, and had improved short-term outcome of less anastomotic leakage compared to high-tie (HT), possibly due to better preservation of blood supply. The 3- and 5-year long-term overall survival and disease-free survival did not differ significantly between the LT and HT groups. Thus, our findings provide evidence for safety and feasibility for low-tie laparoscopic anterior resection for rectal cancer, maintain the oncological principle of adequate lymph node dissection around the inferior mesenteric artery, had fewer leakage compared to high-tie with and comparable long-term overall and disease-free survival.

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Disclosure

The authors declare no conflicts of interest for this work.

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