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High Versus Low Ligation of the Inferior Mesenteric Artery During Rectal Resection for Cancer: Oncological Outcomes After Three Years of Follow-Up From the HIGHLOW Trial

Giulio M. Mari, MD,* Jacopo Crippa, MD,† Pietro Achilli, MD,† Isacco Montroni, MD,‡ Giampaolo Ugolini, MD,‡ Giovanni Taffurelli, MD,‡ Eugenio Cocozza, MD,§ Giacomo Borroni, MD,§ Francesco Valenti, MD,‖ Francesco Roscio, MD,¶ Giovanni Ferrari, MD,# Matteo Origi, MD,# Walter Zuliani, MD,** Raffaele Pugliese, MD,†† Andrea T. M. Costanzi, MD,‡‡ Abe Fingherut, MD,§§ and Dario Maggioni, MD*

Objectives: To determine the disease-free survival (DFS), disease-specific survival (DSS), and recurrence in patients who underwent laparoscopic low anterior rectal resection with total mesorectal excision (TME) with either high or low ligation of the inferior mesenteric artery (IMA).

Background: The level of IMA ligation during anterior rectal resection with TME is still a matter of debate, especially in terms of oncological adequacy.

Methods: Between June 2014 and December 2016, patients scheduled to undergo elective laparoscopic low anterior resection (LAR) and TME in 6 Italian nonacademic hospitals were randomized into 2 groups in the HIGHLOW Trial (ClinicalTrials.gov Identifier: NCT02153801) according to the level of IMA ligation: high ligation (HL) versus low ligation (LL). DFS, DSS, and recurrence were inquired. Recurrence was determined at 3, 6, 9, and 12 months and every 6 months thereafter. Patients and tumor characteristics as well as surgical outcomes were analyzed to identify risk factors for recurrence.

Results: One hundred ninety-six patients from the HIGHLOW trial were analyzed. Median follow-up for DFS was 40.6 (interquartile range [IQR], 6–64.7) and 40 (IQR, 7.6–67.8), while median follow-up for DSS was 41.2 (IQR, 10.7–64.7) and 42.7 (IQR, 6–67.6) in the HL and LL groups, respectively. The 3-year DFS rate of HL and LL patients was 82.2% and 82.1% ($P = 0.874$), respectively. The 3-year DSS for HL and LL patients was 92.1% and 93.4% ($P = 0.897$), respectively. There was no statistically significant difference in the local recurrence rate (2% HL vs 2.1% LL), in the regional recurrence rate (3% HL vs 2.1% LL), and in the distant recurrence rate (12.9% HL vs 13.7% LL). Multivariate analysis found conversion to open surgery (hazard ratio [HR], 3.68; $P = 0.001$) and higher stage of disease (HR, 7.73; $P < 0.001$) to be significant determinant for DFS.

Conclusions: The level of inferior mesenteric artery ligation during LAR and TME for rectal cancer does not affect DFS, DSS, and recurrence.

Keywords: disease-free survival, disease-specific survival, inferior mesenteric artery, laparoscopic surgery, low ligation, rectal cancer.

*From the *Laparoscopic and Oncological General Surgery Department, ASST Monza, Desio Hospital, Desio MB, Italy; †General Surgery Residency Program, University of Milan, Milan, Italy; ‡Colorectal Surgery, Department of Surgery, Ospedale per gli Infermi Faenza, Faenza, Italy; §ASST Sette Laghi, Surgical Oncology and Minimally Invasive Unit, Varese, Italy; ‖General Surgery Department, Humanitas Gavazzeni, Bergamo, Italy; ¶Division of General Surgery, ASST Sette Laghi, Galmarini Hospital, Tradate VA, Italy; #Division of Oncologic and Mini-Invasive General Surgery, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; **Humanitas Mater Domini Clinical Institute, General Surgery, Castellanza VA, Italy; ††AIMS Academy, Milan, Italy; ‡‡General Surgery Department, ASST Lecco, San Leopoldo Mandic Hospital, Merate, Italy; and §§Surgical Research, Department of Surgery, Medical University of Graz, Austria and Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai Minimally Invasive Surgery Center, Shanghai, People's Republic of China.*

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Reprint: Pietro Achilli, MD, University of Milan—Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Via Sforza 35, 20122 Milano, Italy. E-mail: pietro.achilli89@gmail.com.

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INTRODUCTION

The standard surgical approach for extraperitoneal rectal cancer is low anterior rectal resection (LAR) with total mesorectal excision (TME).[1] The level of inferior mesenteric artery (IMA) ligation, however, remains a highly debated issue and has been reported to affect functional outcomes, anastomotic leak rates, and oncological adequacy.[2] Several recent publications have compared genitourinary function, bowel function, and anastomotic leak rate in patients undergoing high ligation (HL) or low ligation (LL) of the IMA during LAR + TME[3–6] while

Key Points

Question: Does the level of inferior mesenteric artery (IMA) ligation have an impact on disease-free survival (DFS), disease-specific survival (DSS), and recurrence in patients who underwent low anterior resection (LAR) and total mesorectal excision (TME) for rectal cancer?

Findings: This analysis after 3 years of follow-up of patients enrolled in the HIGHLOW Trial (ClinicalTrials.gov Identifier: NCT02153801) shows that the level of IMA ligation during LAR and TME for rectal cancer does not affect DFS, DSS, and recurrence.

Meaning: The results of the present analysis suggest that when an oncologically adequate intrapelvic dissection is performed, the level of ligation of the IMA is not a main determinant for survival among patients submitted to LAR and TME for rectal cancer.

data on oncological consequences are sparse.[7–9] The most recent meta-analysis suggests that there is no statistically significant difference in lymph nodes harvest or 5-year overall survival (OS) between the 2 techniques.[10–12] However, the level of evidence is low because all 8 studies included were retrospective cohort studies, and to date, no randomized studies reporting long-term results are available.

In 2019, the HIGHLOW trial was published in *Annals of Surgery* with the aim to investigate the genitourinary function of patients undergoing LAR + TME according to high or low tie of the IMA.[3] Patients in the LL group reported better genitourinary function, while anastomotic leak and postoperative complication rates were similar between groups. There was no difference in surgical surrogates for oncologic adequacy (number of harvested lymph nodes, Quirke score of mesorectal quality, distal, and circumferential margins) between the 2 techniques. Long-term oncological outcomes from the HIGHLOW trial are awaited to assess whether HL and LL are comparable from an oncological point of view.

The aim of this study is to compare the oncological outcomes of the patients enrolled in the HIGHLOW randomized clinical trial (ClinicalTrials.gov Identifier: NCT02153801)[3] after 3 years from the conclusion of the trial.

METHODS

Between June 2014 and December 2016, patients scheduled to undergo elective laparoscopic LAR + TME in 6 Italian nonacademic hospitals in Northern Italy were randomized into 2 groups in the HIGHLOW Trial according to the level of IMA ligation: high versus low tie of IMA. Patients were randomly assigned to HL or LL of the IMA. The random allocation was generated using a computerized randomization system (www.random.org) and was performed using sealed envelopes. In case of LL, preservation of the left colic artery had to be proven by pathological examination, demonstrating the absence of the left colic artery in the specimen of patients undergoing the LL technique. During LL, apical lymph nodes were dissected from the superior aspect of the IMA with a standardized approach that all participating surgeons were trained for, meant to preserve the hypogastric neural plexus on the inferior portion of the origin of the IMA. The operative techniques for HL and LL were previously described. In the LL technique after the pelvic peritoneum is opened below the sacral promontory, the dissection of the peritoneum from the aortic plane goes upward and then laterally toward the sigmoid colon. The left colic artery is identified and preserved. The superior rectal artery is divided. The superior aspect of the IMA is cleared from lymphatic tissue, while the inferior aspect of the IMA and the surrounding hypogastric plexus are left in place (Fig. 1).[13] Oncologic adequacy of HL and LL procedures was evaluated by comparing the difference in harvested lymph nodes and Quirke classification of quality of the mesorectum.[14]

Details of the study design and short-term outcomes have been previously published.[3] The primary outcome of the original HIGHLOW trial was to investigate a difference in genitourinary function using questionnaires and objective evaluations. Postoperative complications were assessed using the Clavien–Dindo classification.[15] Conversion to open surgery, anastomotic leak, and other short-term outcomes were collected to investigate differences between groups.

All patients were followed every 3 months for the first year and every 6 months thereafter for the next 2 years according to the National Comprehensive Cancer Network Guidelines.[11] Patients were followed-up within a multidisciplinary setting involving surgeons, oncologists, radiologists, and pathologists. Patients were given a physical examination every 6 months for a total of 5 years. A chest–abdominal–pelvic computed tomographic (CT) scan was performed every 6 months for 2 years, then once a year

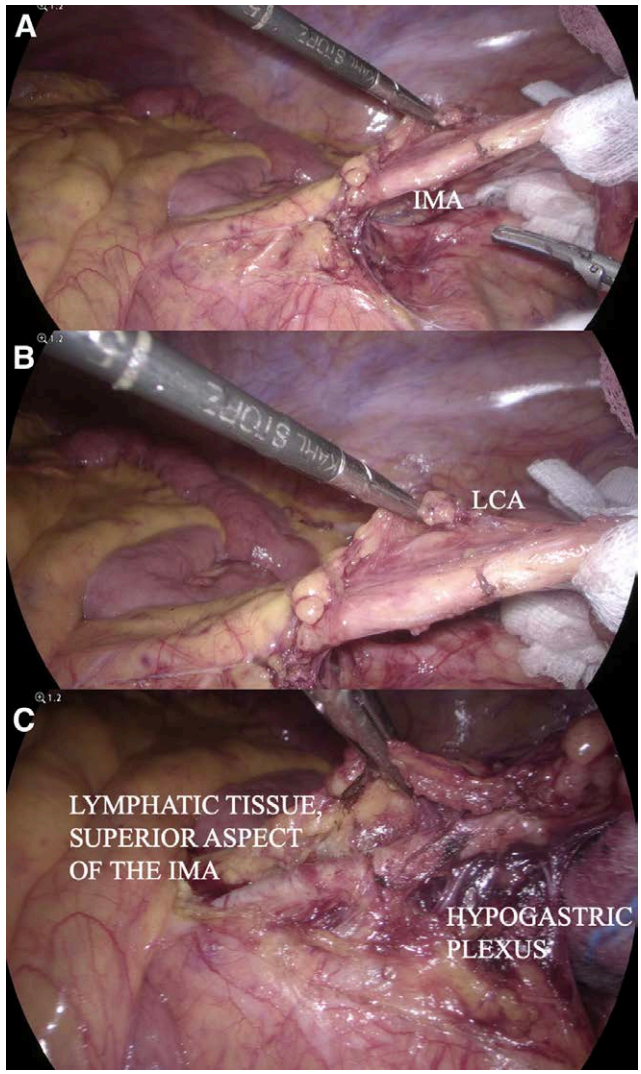

FIGURE 1. A, Inferior mesenteric artery exposure. B, Left colic artery dissection. C, Hypogastric plexus preservation and isolation of the lymphatic tissue on the superior aspect of the IMA.

for a total of 5 years from surgery. A colonoscopy was performed for each patient within 1 year after surgery. If an advanced adenoma was found, a colonoscopy was repeated within 1 year. If no advanced adenoma was found, a colonoscopy was repeated after 3 years. Carcinoembryonic antigen analysis was performed every 6 months for a total of 5 years. An increment in carcinoembryonic antigen levels was an indication to perform a CT scan outside the ordinary schedule. If metachronous metastases were found at radiological evaluation, a PET/CT scan was performed to confirm resectability and to evaluate the extension of the disease. Data on OS, disease-free survival (DFS), disease-specific survival (DSS), local recurrence (LR), and distant metastasis (DM) were prospectively collected for each patient.

An LR was defined as tumor recurrence within the lower pelvis, a regional recurrence was defined as tumor recurrence within pelvic lymph nodes, and DM was defined as tumor recurrence elsewhere. A recurrence was diagnosed through radiologic imaging. A biopsy was performed when the radiological imaging was doubtful and when it was deemed to be necessary and feasible by the multidisciplinary team. OS was calculated from the date of surgery to the last date of follow-up or death from any cause. DSS was calculated from the date of surgery to the last date of follow-up or death from cancer. DFS was defined as the time elapsed from the date of surgery until a LR or DM occurred.

Statistical Analysis

Analysis was performed according to the intent-to-treat basis. Time-to-event Kaplan–Meier curves were determined for DFS and DSS and compared with the log-rank test. Cox proportional-hazard models were adjusted by tumor location (low, middle, and high rectum), free circumferential margin of at least 1 mm, Clavien–Dindo complication rate[15] equal or higher than 3, completeness of the pathological specimen according to Quirke,[14] and disease stage. Rates of local, distant, and regional recurrence were presented as frequencies and percentages. In the original HIGHLOW Trial, a sample size of 212 patients enabled a 2-tailed Fisher exact test applied to 2 cohorts of 100 patients each to have 84.45 power in estimating a 20% difference in the incidence of genitourinary dysfunction ($\alpha = 0.05$, $\beta = 0.1555$).[3] The level of significance was set at 5% with 2-sided tests. All statistical analyses were performed using the statistical software Statistical Package for the Social Sciences (SPSS) software (version 22, SPSS, Chicago, IL).

RESULTS

One hundred ninety-six patients from the HIGHLOW trial were analyzed. Patients' characteristics are described in Table 1.

From the original HIGHLOW study, there were no significant difference in the mean number of harvested lymph nodes between the groups. Apical lymph nodes were collected separately from the specimen in the LL group and within the specimen in the HL group. There were no patients with apical lymph node metastasis in either group. No left colic artery stumps were found in the specimens of all LL patients, demonstrating that the LL technique had been performed correctly. The completeness of the mesorectum according to Quirke classification did not differ and was higher than 90% in both groups. The incidence of postoperative stage III tumors was greater in the HL group.[3]

Median follow-up for OS was 41.2 (interquartile range [IQR], 35.2–55.6) and 43 (IQR, 33.7–55.2) months while for DFS was 40 (IQR, 28.1–54.7) and 40 (IQR, 30.7–51.1) months in the HL and LL groups, respectively.

The number of patients with more than 3 years of follow up was 134 (68.4%), 31 (15.8%) patients died, and 31 (15.8%) did not complete the surveillance protocol. The 3-year OS rate of HL and LL patients was 83.1% and 85.2% ($P = 0.735$) and the DFS was 83.8% and 84.2% ($P = 0.567$), respectively, with no statistical difference (Figs. 1, 2). The 3-year DSS for HL and LL patients was 90.2% and 92% ($P = 0.895$), respectively, with no statistical difference found between the 2 groups (Figs. 3, 4).

Laparotomic conversion happened in 10 patients (9.5%) in the LL group and in 10 patients (10.5%) in the HL group ($P > 0.05$). Reasons for conversion were uncontrolled bleeding in 10 patients (50%), tenacious adhesions in 7 patients (35%), and unclear dissecting plane in 3 patients (15%).

A total of 3 LR occurred. There was no statistically significant difference in LR rate between groups (2% HL vs 2.1% LL; $P = 0.958$). Two cases of LR after HL occurred in patients with an incomplete mesorectal fascia at the pathological examination. In the LL group, LR happened in one patient with an incomplete mesorectum fascia at the pathological examination and in one patient with a nearly complete mesorectum fascia at the pathological examination.

There was no statistically significant difference found in the regional recurrence rate between the 2 groups (3.25% HL vs 2.1% LL; $P = 0.719$). All regional lymph node recurrences occurred in patients who were stage IIIb, irrespective of the allocation.

No statistically significant difference was found in the distant recurrence rate (13 HL vs 13 LL; $P = 0.970$) nor in the sites of the recurrences (mainly liver and lung in both groups). In the HL group, distant recurrence occurred in 2 patients with a stage I, in 1 patient with stage II, and in 10 patients with stage III rectal cancer. In the LL group, distant recurrence occurred in 2 patients with stage I, 2 patients with stage II, and 9 patients with stage III rectal cancer. There was no difference in stage-specific recurrence between groups.

Upon univariate analysis, conversion to open surgery (hazard ratio [HR], 2.68; CI 95%, 1.1–6.2; $P = 0.037$) and stage III disease (HR, 2.5; CI 95%, 1.1–5.7; $P = 0.024$) were significantly associated with OS. Quirke score incomplete (HR, 4.66; CI 95%, 1.1–19.6; $P = 0.0360$), adjuvant (HR, 5.54; CI 95%, 2.3–13.3; $P < 0.001$) and neoadjuvant therapy (HR, 3.27; CI 95%, 1.7–6.4; $P < 0.001$), stage III disease (HR, 14.3; CI 95%, 5.0–40.9; $P < 0.001$), middle (HR, 2.21; CI 95%, 1.1–4.3; $P = 0.021$) and low (HR, 7.66; CI 95%, 1.0–57.6; $P = 0.048$) rectal cancer, conversion to open (HR, 4.94; CI 95%, 2.4–10.1; $P < 0.001$), and CD ≥3 (HR, 3.57; CI 95%, 1.67–7.63; $P = 0.003$) were all significantly associated with DFS upon univariate analysis. The level of ligation was not significantly associated with either OS or DFS.

After multivariate analysis, conversion rate was found to be a significant determinant for DFS (HR, 3.9; CI 95%, 1.85–8.22; $P = 0.003$), but not for OS (HR, 2.4; CI 95%, 0.9–5.7; $P = 0.067$)]. At multivariate analysis, stage III rectal cancer

Table 1.

Tumor Characteristics and Outcomes

	Total Patients, n = 196 (100%)	High Ligation, n = 101 (51.5%)	Low Ligation, n = 95 (48.5%)	*P*
Neo adjuvant CRT	55 (28.1)	30 (29.7)	25 (26.3)	0.635
Compliance to neo adjuvant CRT				
Adjuvant chemotherapy	96 (49)	56 (55.4)	40 (42.1)	0.065
Compliance to adjuvant chemotherapy				
Site of tumor in the rectum				
Upper	23 (11.7)	15 (14.8)	8 (8.4)	
Medium	116 (59.2)	62 (61.4)	54 (56.8)	0.003
Low	57 (29.1)	24 (23.8)	33 (34.7)	
Conversion from lap to open	21 (10.7)	10 (9.9)	10 (10.5)	1.000
Clavien–Dindo, CD ≥ 3	20 (10.2)	11 (10.9)	9 (9.5)	0.816
Quirke completeness of TME				
Complete	178 (90.8)	91 (90.1)	87 (91.6)	
Nearly complete	15 (7.7)	8 (7.9)	7 (7.4)	0.858
Incomplete	3 (1.5)	2 (2)	1 (1)	
Circumferential margin ≤1 mm	19 (9.7)	11 (10.9)	8 (8.4)	0.560
Stage of rectal cancer				
Stage 1	96 (49)	41 (40.6)	55 (57.9)	0.016
Stage 2	43 (21.9)	22 (21.8)	21 (22.1)	
Stage 3	57 (29.1)	38 (37.6)	19 (20)	

CD, Clavien–Dindo; TME, total mesorectal excision.

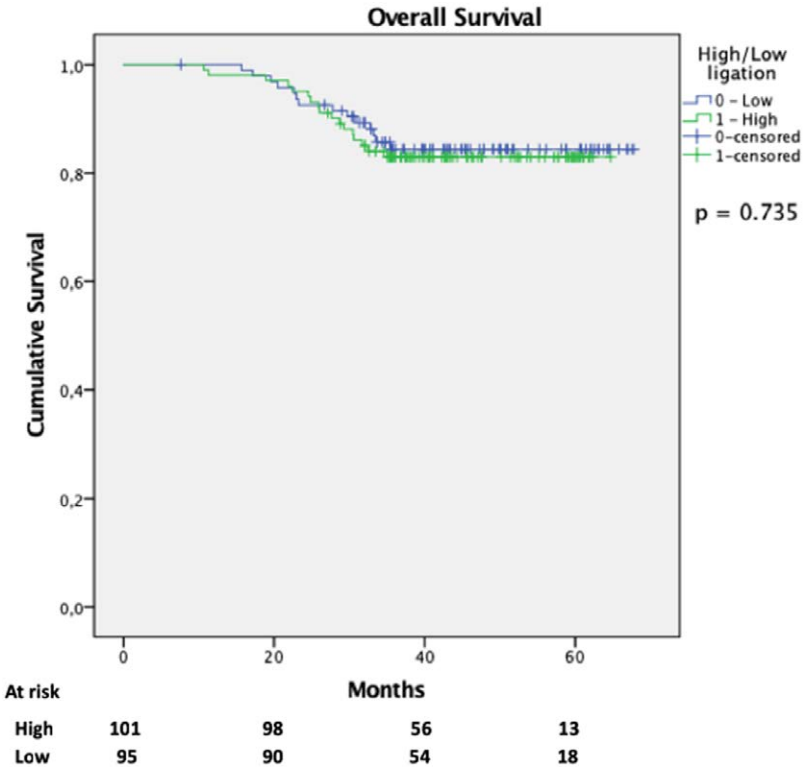

FIGURE 2. Kaplan Meyer curve for overall survival.

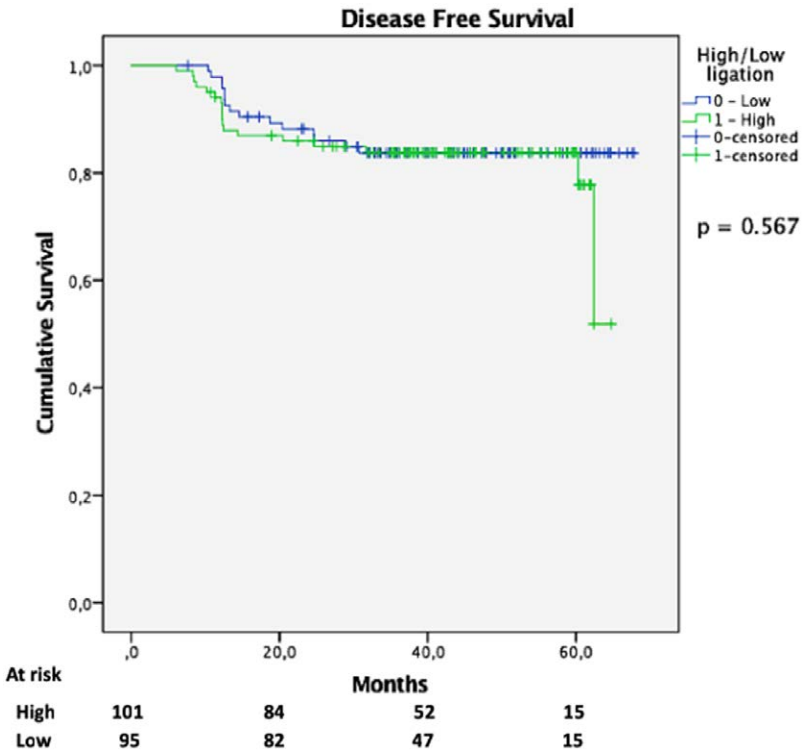

FIGURE 3. Kaplan Meyer curve for disease-free survival.

retained significance for both OS (HR, 2.32; CI 95%, 1.0–5.38; $P = 0.047$) and DFS (HR, 12.97; CI 95%, 4.44–37.86; $P < 0.001$). The level of ligation did not affect OS and DFS significantly after multivariate analysis (Table 2).

DISCUSSION

The analysis of oncological outcomes after 3 years from the conclusion of the HIGHLOW trial found that the DFS, DSS, and local and distant recurrence rates were not found to be different

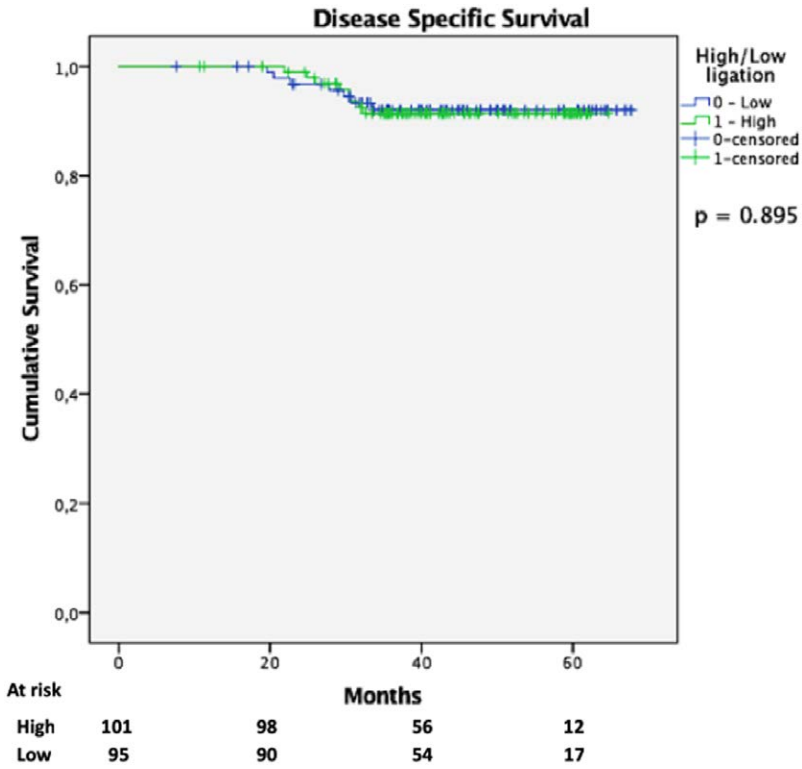

FIGURE 4. Kaplan Meyer curve for disease-specific survival.

Table 2.

Factors Affecting OS and DFS: Multivariate Analysis

Factors	OS HR (CI 95%)	*P*	DFS (CI 95%)	*P*i
IMA ligation				
High vs low	1.00 (0.48–2.07)	0.996	0.74 (0.37–1.48)	0.404
Conversion from lap to open				
Yes vs no	2.4 (0.99–5.67)	0.067	3.9 (1.85–8.22)	0.003
Stage of rectal cancer (Ref. Stage 1)				
Stage 3	2.32 (1.00–5.38)	0.047	12.97 (4.44–37.86)	<0.001
Stage 2	1.34 (0.50–3.61)	0.554	1.62 (0.40–6.65)	0.501

DFS, disease-free survival; HR, hazard ratio; IMA, inferior mesenteric artery; OS, overall survival.

between patients who had HL or LL of IMA during laparoscopic LAR for extraperitoneal rectal cancer.

Based on our findings, it seems that the main determinant of survival was not the level of vascular ligation, but the quality of the intrapelvic dissection. Indeed, all cases of local relapse occurred in patients who had an incomplete or nearly complete mesorectum excision, according to the Quirke criteria.[14] This is in line with the randomized trials comparing open to minimally invasive LAR reporting a 1.8% and 2.1%, and 3.1% and 5.4% for LR rates at 2 years for stage II or III rectal cancer, respectively, with no difference in circumferential margin involvement rate between the 2 techniques.[16,17] These results are in concordance with an earlier randomized clinical trial that went unnoticed because the words "high tie" and "low tie" were not mentioned specifically in the title, abstract, or even in the text.[18] Indeed, this trial compared the 10-year survival and early complication rates after curative resection for carcinoma of the left colon by "left hemicolectomy" or "left segmental colectomy", the terms that were in vogue at that time. Of note, the 2 groups were specifically described as undergoing high or low tie of the IMA, respectively. At 12 years of follow up, there was no statistically significant difference in "survival" between the patients in either group irrespective of Dukes stage (the terms "disease-free survival" or "disease-specific survival" had not yet been clearly defined in 1994). The median survival rate was 10 years, with no statistically significant difference between the 2 groups. The only difference noted was increased frequency of bowel movements during the first postoperative year for LCG (or HL), but this difference disappeared after 12 months.

With regard to distant recurrence, previous studies were mainly retrospective. One recent cohort study did not report any statistically significant differences in surgical, histological, short-term, or long-term oncological outcomes between patients treated with either HL or LL.[19] Similarly, in a case–control study comparing HL and LL approach, where LL was associated with IMA root lymph node retrieval, there was no statistically significant intergroup difference in recurrence or OS rates. Conversely, the DFS in the LL group was lower than that in the HL group.[20] The French randomized study did not individualize LR.[18]

Matsuda et al[5] conducted a randomized clinical trial comparing defecatory function according to whether patients underwent HL or LL during anterior resection for rectal cancer. However, even if this study tended to show that the level of ligation of the IMA did not affect defecatory function or the rate

of postoperative complications, this study was underpowered as at 3 months, only 88 of the 100 patients necessary for the power calculation were assessed (high [n = 47], low [n = 41]). These same authors published the oncological follow-up of the same group of patients 2 years later.[7] Again, even though the study concluded that the ligation level of the IMA in rectal cancer did not influence the oncological outcomes, these conclusions were not justified according to the methodology used. They advocated large-scale RCTs to conclude this issue[7].

Fujii et al[6] conducted a randomized trial comparing the anastomotic leak rate between HL and LL. The sample size was tailored on that primary endpoint. The study was stopped prematurely because of slow accrual. However, it did not detect any significant differences in terms of anastomotic leak rate between the 2 groups. Five-year overall survival rate was listed as a secondary endpoint. The trial did not report a statistically significant difference in the 5-year relapse-free survival rate and in the 5 years overall survival rate.[6] The authors did not power the study on oncological outcomes nor discuss a possible influence of underpowered analysis in the limitations.

Our protocol specified that all patients should undergo lymph node dissection at the root of the IMA irrespective of the level of ligation. The appropriate extent of lymphadenectomy at the origin of the IMA for lower rectal carcinoma remains an unsolved issue. The rationale in favor or against it has been debated for years.[18] Several authors argue that HL alone could adequately control and improve survival for left colonic cancer because the root lymph nodes are involved in more than 10% of cases, the possibility of skip lesions, or control of retrograde lymph flow, improved survival of patients with involvement of more than 5 lymph nodes as well as providing extra length for a tension-free anastomosis.[21–23] Those who say root lymph node dissection is not necessary proclaim less postoperative mortality and morbidity with LT and the absence of definitive convincing arguments in favor of longer survival with HL.[24] No positive apical lymph nodes were found in either group in our study.[3]

Conversion to laparotomy was found to be associated with a greater risk of recurrence. This contrasts with the data from a meta-analysis performed in 2017.[25] Worse DFS survival in patients where conversion was necessary might be related to the stage of disease more than to conversion itself. Indeed, stage III rectal cancer is associated with worse DFS in itself,[17] and 40% of the conversions occurred among patients with stage III disease. The size of the tumor may also be a plausible explanation, all the more that the definition of conversion for specimen extraction has never been formally closed.[26]

The sample size of the HIGHLOW trial was calculated to investigate functional outcomes rather than oncological outcomes, and this represents the main limitation of the study. The calculation of the sample size necessary to perform a powered study aimed to compare OS, DSS, and DFS among patients undergoing laparoscopic LAR + TME according to HL or LL should be performed with a noninferiority criterion of the LL technique compared to the HL one. The number of patients would therefore grow significantly, making even a multicenter study likely to be excessively long. Despite this, planning an ad hoc randomized study tailored on the oncological outcomes remains the only way to achieve a sufficient statistical probability to adequately compare LL and HL in terms of cancer survival. Despite this, the HIGHLOW trial remains one of the largest studies on HL versus LL of the IMA reporting on oncological outcomes.

Performing the LL technique could become a risk factor for understaging stage III rectal cancer, thus producing a "high-risk LL-related stage II rectal cancer." Although possible, this eventuality seems unlikely given the similar node counts in the 2 groups and the lymph nodes sampling of the superior aspect of the root of the IMA performed in the LL group.

In conclusion, LL of the IMA does not seem to impair oncological outcomes compared to HL after 3 years from the conclusion of the HIGHLOW trial. The purported advantages of HL have to be weighed against increased morbidity. Data are awaited to confirm these findings when a longer follow-up will be available for analysis.

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