Low Tie Compared to High Tie Vascular Ligation of the Inferior Mesenteric Artery in Rectal Cancer Surgery Decreases Postoperative Complications Without Affecting Overall Survival

MIHANE NAYERI^{1*}, OTHMAN ISKANDER^{1*}, NICOLAS TABCHOURI¹, ALICE ARTUS¹,
NICOLAS MICHOT¹, OLIVIER MULLER¹, URS GIGER-PABST², PASCAL BOURLIER¹,
AURORE KRAEMER-BUCUR¹, THIERRY LECOMTE³, EPHREM SALAME¹ and MEHDI OUAISSI¹

¹Department of Digestive, Oncological, Endocrine, Hepato-Biliary,
Pancreatic and Liver Transplant Surgery, Trousseau Hospital, Tours, France;

²Department of General-, Visceral- and Transplant Surgery, University of Münster, Münster, Germany;

³Department of Hepatogastroenterology and Digestive Oncology, Trousseau Hospital, Tours, France

Abstract. *Background/Aim:* The aim of this study was to determine the clinical impact of low tie ligation (LT) of the inferior mesenteric artery (IMA) below the left colic artery versus high tie ligation (HT) at the origin of the IMA in patients undergoing rectal cancer surgery. *Patients and Methods:* Between January 2005 and December 2017, all consecutive patients who underwent rectal resection for non-metastatic cancer were retrospectively included. Patients who had LT were compared to those who had HT. *Results:* Overall, 200 patients were identified (101 HT and 99 LT). Postoperative 30-day mortality rate was nil in both groups. There were significantly higher severe postoperative complications in HT versus LT patients (Clavien-Dindo III-IV) (18.8% vs. 9.1%, $p=0.048$). Median follow-up was 38.5 months and overall survival at 5 years was 91.5% and there was no difference between the two groups (90.1% vs. 92.9%; HT vs. LT $p=0.640$). *Conclusion:* LT ligation of IMA significantly decreased the severe postoperative complication rate without affecting recurrence-free or overall survival.

The multimodal management of rectal carcinoma has improved in the last twenty years and is now well standardized.

*These Authors contributed equally to the present study.

Correspondence to: Professor Mehdi Ouaiissi, Department of Digestive, Oncological, Endocrine, Hepato-Biliary, Pancreatic and Liver Transplant Surgery, Chambray les Tours, Colorectal Surgery Unit, Trousseau Hospital, Avenue de la République, Chambray les Tours, France. Tel: +33 0247474634, Fax: +33 0247474641, e-mail: m.ouaiissi@chu-tours.fr

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Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) has become the gold standard for locally advanced rectal carcinoma (1, 2-4). However, even if standardized TME and neoadjuvant treatment are well defined in rectal cancer management, the level of ligation of the inferior mesenteric artery (IMA) is still debated. Indeed, two different levels of ligation are commonly used, depending on the surgeon's preference. High-tie (HT) ligation is obtained with the transection of the IMA 1 cm distally from the aorta, associated with the transection of the inferior mesenteric vein (IMV) at the inferior border of the pancreas. Low-tie (LT) ligation is on the other hand obtained with the transection of the IMA 1 cm distally to the origin of the left colic artery (LCA) to allow the preservation of the LCA. Theoretical advantages proposed by the proponents of HT ligation are a more extended lymphadenectomy with improved oncological results (5, 6) with a more standardized surgical technique and better reproducibility (7). Furthermore, the HT ligation approach would lead to an additional gain of length of the lowered colon (8). However, these advantages have never been confirmed so far. Particularly, extended lymphadenectomy has not been associated with improved overall survival, and to our best knowledge, no author has reported that HT ligation is an absolute prerequisite for tension-free anastomosis (9, 10). Moreover, a recent randomized clinical trial demonstrated that HT could increase genitourinary dysfunctions (11). This lack of evidence is mainly due to the heterogeneity of published series (including sigmoid as well as rectal cancer or liver metastases) (5, 6), or to the absence of standardized surgical management (laparoscopic vs. open, with or without neoadjuvant treatment) (12, 13). The aim of this study was, therefore, to compare HT and LT ligation of the IMA, in patients who required total or partial TME for rectal cancer in a tertiary referral center, with emphasis on short- and long-term postoperative outcomes.

Patients and Methods

Population - study design. All patients who had surgery for rectal adenocarcinoma between January 2005 and December 2017 in a tertiary referral center were retrospectively reviewed. The study included patients with high (15-10 cm from anal verge), middle (10-5 cm from anal verge) or low (5-2 cm from anal verge) rectal cancer and had total or partial TME with colorectal or colo-anal anastomosis. All patients who presented with metastatic disease requiring associated surgical procedures (mainly other organ resections), who had previous surgery on the left sided colon or local excision of the rectum were excluded. Furthermore, patients who had previous documented episodes of ischemic disease of the intestine or any abnormality of the digestive vascularization due to atherosclerosis were also excluded, as well as patients who underwent abdominoperineal resection or Hartmann's procedure. The data included demographic variables, primary tumor characteristics and management, operative data, tumor pathology and short- and long-term outcomes. Patients who had HT ligation were compared with those who had LT ligation.

Ethical approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Preoperative work-up. Data were retrospectively retrieved from medical records. Demographic features (gender, age at time of surgery, body mass index), tumor evaluation before neoadjuvant treatment, type of neoadjuvant treatment, pathological and oncological results were collected. Tumor evaluation was based on physical examination with digital rectal exam and anoscopy, serum CEA and CA19-9, total colonoscopy with biopsy, endorectal ultrasound (EUS) and/or pelvic magnetic resonance imaging (MRI), as well as computed tomography (CT).

Neoadjuvant treatment. Preoperative long course radiotherapy consisted of 50.4 Gray, delivered in 25 to 28 fractions, daily, during five to six weeks. Pelvic volume was defined based on tumor characteristics, mesorectum, the ventral side of the sacrum and the hypogastric vessels. L5 and S1 vertebrae determined the upper limit, while the levator ani muscle or the anal verge determined the lower limit, whether patient presented with middle or low rectal cancer. Preoperative chemotherapy was concomitantly administered (oral 5-FluoroUracil (Capecitabine, Xeloda®), 825 mg/m²/day, twice a day) (14). Short course radiotherapy consisted of a total dose of 25 Gray, delivered in five fractions spanning over 5 to 7 days (15).

Pre- and intraoperative course. Bowel preparation consisted of oral mechanical preparation with sodium phosphate or polyethylene glycol at least 3 days before surgery, associated with oral antibiotics (Metroimidazole during five days). A single dose of prophylactic antibiotics was routinely given (750 mg of Cefuroxime) at induction of general anesthesia and was repeated intraoperatively if surgery lasted for >2 h. Deep-vein thrombosis prophylaxis was administered in all patients (consisting of low molecular-weight heparin, 50 UI/kg per day) during 30 postoperative days.

Surgical procedures. Laparoscopy represented the standard approach unless patients presented with T4 tumor or were considered unfit for laparoscopy (anesthetic contraindication), in which case laparotomy was preferred. All procedure steps of rectal cancer resection were standardized, except for AMI level of ligation and splenic flexure mobilization. All patients underwent a standardized proctectomy with total or partial mesorectum excision, 5 to 6 weeks after completion of CRT. Total mesorectal excision was performed as previously described (1). A medial-to-lateral approach was performed in all patients. Ligation of the inferior mesenteric vein (IMV) was performed at the lower part of the pancreas followed by mobilization of the left colon and the splenic flexure (the extent of mobilization was left at the discretion of surgeon). Regarding IMA ligation, HT ligation was obtained with the transection of the IMA 1 cm distally from the aorta while LT ligation was obtained with the transection of the IMA 1 cm distally to the origin of the left colic artery (LCA) allowing for its preservation.

Preservation of LCA was routinely performed by four surgeons (MO, NT, MN, OI). Only, three (3.0%) LT patients (3.0%) required secondary transection of the LCA in order to obtain a tension-free anastomosis. The distal rectum was transected using a linear stapler. The specimen was then removed via a small abdominal incision, and the proximal colon was transected approximately 10 cm above the lesion (16). Termino-terminal or latero-terminal colo-rectal mechanical anastomosis or colo-anal manual anastomosis were performed. A diverting double-loop ileostomy was usually performed. Stoma was usually closed three months later, provided the general condition of the patient was fitting.

Pathological results. Surgical specimens were analyzed using a standardized protocol. Histological evaluation consisted of (yp)TNM staging, circumferential and distal margins (R0, R1 and R2 for complete, microscopically and macroscopically incomplete resections, respectively) in- or complete mesorectal excision status, degree of colloid component, differentiation grade, presence of vascular, lymphatic or perineural emboli. Tumors were staged using the TNM classification according to the 8th edition of American Joint Committee of Cancer (AJCC) (17). An involved circumferential resection margin (CRM) was defined as ≤1 mm between the deepest tumor invasion and the margin of surgical resection inked previously. This included a tumor within a lymph node, as well as a direct tumor extension. Acellular pools of mucin observed on CRM following neoadjuvant CRT were considered as negative margins (18).

Postoperative outcomes. All complication(s) at 30 postoperative days were recorded (including anastomotic leakage, ischemia, abscess, collection, hematoma, bleeding, peritonitis, anastomosis stenosis, infection, cardiorespiratory complication, or death), along with management modalities (medical, radiological, surgical). Postoperative complications were ranked according to the international Clavien Classification (19). Physical examination was performed in all patients at 4-6 weeks following discharge. In-hospital stay was measured from the time of surgery to the date of discharge from hospital. Anastomotic leakage was defined and graded according to the International Study Group of Rectal Cancer (20), with patients divided into three groups for analysis: symptomatic AL (SAL, including grade B and C ALs), asymptomatic radiologic AL (AAL, diagnosed on enema-contrast CT-scan, routinely performed 6 to 8 weeks postoperatively, before

Table I. Demographic and preoperative characteristics.

	High tie	Low tie	Overall	p-Value
N (%)	101 (50.5)	99 (49.5)	200	-
Age (years)	65 (39-88)	68.5 (37-85)	67 (37-88)	0.128
Female/Male	33/68	32/67	65/135	0.957
BMI (kg/m ²)	24 (18-40)	24 (16-60)	24 (16-60)	0.251
ASA Score				
ASA1	56 (55.4)	50 (50.5)	106 (53.0)	0.659
ASA2	40 (39.6)	41 (41.4)	81 (40.5)	
ASA3	6 (6.0)	8 (8.1)	13 (6.5)	
Arteriopathy	4 (4.0)	11 (11.1)	16 (8.0)	0.064
Diabetes	6 (5.9)	17 (17.2)	23 (11.4)	0.013
Rectal tumor location				
High (10-15 cm)	22 (21.6)	31 (31.3)	53 (26.5)	0.220
Middle (5-10 cm)	55 (54.5)	50 (50.5)	105 (52.5)	
Low (0-5 cm)	24 (23.5)	18 (18.2)	42 (21.0)	
Distance from the anal verge (cm)	8 (2-18)	9 (1-17)	8 (1-18)	0.162
Neoadjuvant radiotherapy	75 (74.3)	75 (75.8)	150 (75.0)	0.806
Neoadjuvant chemo-radiotherapy (long course)	70 (69.3)	68 (68.7)	138 (69.0)	0.384
Neoadjuvant radiotherapy (short course)	5 (5.0)	7 (7.1)	12 (6.0)	0.384

BMI: Body mass index.

considering stoma reversal) and without AL (WAL). Any clinical (sepsis, peritonitis, emission of gas, pus, or feces from the pelvic drain, purulent discharge per anus, or rectovaginal fistula) and/or biological suspicion of AL led to an early CT-scan assessment.

Long term outcome. Postoperative follow-up included clinical, biochemical, and radiological assessments every 3 months during the first postoperative year, every 6 months thereafter up to 5 years postoperatively and every year thereafter up to 10 years postoperatively. Surviving patients were assessed for disease recurrence and site of recurrence. Follow-up information was obtained from medical records, outpatient clinic, and/or through phone interview. Follow-up was updated to December 28th 2018.

Statistical analyses. Statistical analyses were performed using IBM SPSS Statistics version 20 (IBM SPSS Inc., Chicago, IL, USA). Baseline characteristics of the studied population, intraoperative and pathological characteristics as well as postoperative outcome were analyzed. Categorical variables were compared using the χ^2 test or Fischer's exact test when appropriate. Continuous variables were compared using Student *t*-test or Mann-Whitney test when appropriate. The Kaplan-Meier method was used to estimate recurrence-free survival (RFS) and OS, which were compared using the Log rank test. Statistical significance was accepted at the 0.05 level.

Results

Population. Overall, 200 patients were included in the study, of which 99 had LT ligation and 101 HT ligation. Demographic characteristics are reported in Table I. Both groups were comparable except for diabetes, which was significantly less frequent in the HT group (5.9% vs. 17.2%

in HT group; $p=0.013$). Overall, rectal tumor location was considered high, middle or low rectum in 53 (26.5%), 105 (52.5%) and 42 (21.0%) patients, respectively, and no differences were found between HT and LT groups ($p=0.220$). Neoadjuvant treatment was performed in 150 (75%) patients with no difference found between both groups (74.3% in HT group vs. in 75.8% LT group; $p=0.806$). Both groups were also comparable in terms of the exact type of neoadjuvant treatment.

Surgical procedure. Intraoperative parameters are reported in Table II. Laparoscopic resection was performed in 188 (94%) patients with comparable rates between both groups ($p=0.080$). Total mesorectal excision was complete in 149 (74.5%) patients with no difference found between both groups ($p=0.257$). Overall, conversion was required in 45 (22.5%) patients and was significantly lower in HT group (16.8% vs. 28.3% in LT group, $p=0.017$). Splenic flexure mobilization was performed in 162 (81%) patients and was significantly more frequent in HT group (92.1% vs. 69.7% in LT group, $p<0.001$). Latero-terminal anastomosis was performed in 93 (46.5%) patients with a significantly higher rate in the HT group (54.4% vs. 38.4%; $p=0.024$) whereas 107 (53.5%) patients had termino-terminal anastomosis. Manual colo-anal anastomosis was performed in 29 (14.5%) patients with no statistical difference found between both groups ($p=0.228$). Intraoperative diverting stoma was required in 179 (89.5%) patients with a similar rate in both groups ($p=0.780$). **Morbidity and mortality.** Postoperative details are reported in Table II. Thirty-day mortality rate was nil in both groups.

Table II. Intraoperative and postoperative parameters.

	High tie	Low tie	Overall	p-Value
N (%)	101 (50.5)	99 (49.5)	200	
Laparoscopic	98 (97.0)	90 (90.9)	188 (94.0)	0.080
Conversion to laparotomy	17 (16.8)	28 (28.3)	45 (22.5)	0.017
Splenic flexure mobilization	93 (92.1)	69 (69.7)	162 (81.0)	<0.001
Complete TME	79 (78.2)	70 (70.7)	149 (74.5)	0.257
Near complete TME	22 (21.7)	29 (29.3)	51 (25.5)	
Anastomosis type				
Latero-terminal rectal anastomosis	55 (54.4)	38 (38.4)	93 (46.5)	0.024
Termino terminal rectal anastomosis	46 (45.5)	61 (61.6)	107 (53.5)	
Colo-anal manual anastomosis	18 (17.8)	11 (11.1)	29 (14.5)	0.228
Diverting stoma	91 (90.1)	88 (88.9)	179 (89.5)	0.780
Postoperative complication rates				
Overall	44 (43.5)	30 (30.3)	74 (37)	0.058
CD I-II	25 (24.7)	21 (21.2)	46 (23.0)	0.651
CD III-IV	19 (18.8)	9 (9.1)	28 (14.0)	0.048
Anastomotic leak	24 (23.7)	15 (15.1)	39 (19.5)	0.153
Asymptomatic	6 (5.9)	4 (4)	10 (5.0)	0.747
Symptomatic	18 (17.8)	11 (11.1)	29 (14.5)	0.226
Pelvic collection	15 (14.9)	7 (7.1)	22 (11.0)	0.079
Redo abdominal surgery	9 (8.9)	6 (6.6)	15 (7.5)	0.593
Local drainage	2 (2.0)	3 (3.0)	5 (2.5)	0.498
Permanent stoma	17 (16.8)	14 (14.1)	31 (15.5)	0.697
Median Hospital stay (days)	12 (4-77)	11 (3-80)	11 (3-80)	0.339

Table III. Pathological findings and oncological results.

	High tie	Low tie	Overall	p-Value
N (%)	101 (50.5)	99 (49.5)	200	
Lymph nodes	18 (2-52)	18 (2-76)	18 (2-76)	0.720
Tumor diameter (mm)	27 (0-140)	25 (0-110)	25 (0-140)	0.295
Positive margins	5 (5.0)	4 (4.0)	9 (4.5)	0.748
Distal	3 (3.0)	1 (1.0)	4 (2.0)	0.621
Circumferential	5 (5.0)	4 (4.0)	9 (4.5)	1.000
T stage				
No residual tumor	16 (15.8)	12 (12.1)	28 (14.0)	
T1	15 (14.9)	15 (15.2)	30 (15.0)	
T2	31 (30.7)	26 (26.3)	57 (28.5)	0.744
T3	35 (34.7)	43 (43.4)	78 (39.0)	
T4	4 (4.0)	3 (3.0)	7 (3.5)	
N stage				0.808
N0	78 (77.2)	74 (74.7)	152 (76.0)	
N1	18 (17.8)	21 (21.2)	39 (19.5)	
N2	5 (5.0)	4 (4.0)	9 (4.5)	
Adjuvant therapy	25 (24.7)	27 (27.7)	52 (26.5)	0.806
Oncological results				
Median of follow-up (months)	40.7 (1-153)	33.9 (1-136)	38.5 (1-153)	0.730
3-year OS (%)	94.1	97.0	95.5	0.640
5-year OS (%)	90.1	92.9	91.5	
3-year RFS (%)	84.2	78.8	81.5	0.417
5-year RFS (%)	83.2	77.8	80.5	
Recurrence (n)	17 (16.8)	22 (22.2)	39 (19.5)	0.343

OS: Overall survival; RFS: recurrence-free survival.

Figure 1. Overall survival according to IMA ligation level. Low ligation (LT) group (solid line) and High ligation (HT) group (dashed line).

Figure 2. Recurrence-free survival according to IMA ligation level. Low ligation (LT) group (solid line) and High ligation (HT) group (dashed line).

Overall, 74 (37.0%) patients presented with postoperative complications (43.5% in HT group vs. 30.3% in LT group; $p=0.058$). There were significantly more severe postoperative complications (grade III-IV) in HT patients (18.8% vs. 9.1%, $p=0.048$). Anastomotic leaks were found in 39 (19.5%) patients and were more frequent, although statistically not significant, in the HT group (23.7% vs. 15.2%, $p=0.153$). Postoperative anastomotic leakage (AL) occurred in 39 (19.5%) patients, of which 29 patients (14.5%) had symptomatic leak (SAL) and 10 patients (5.0%) presented with an asymptomatic leak (AAL). Repeat abdominal surgery was performed after a median of seven days (range=3-22 days) in 12 (41.4%) patients (anastomosis resection and colostomy placement, $n=6$ and peritoneal lavage with anastomosis repair and drainage, $n=6$), of which three presented with one or more organ dysfunction and were admitted into intensive care unit. Trans-anal drainage was performed in five (17.2%) patients, of which three underwent general anesthesia. Overall 11 (37.9%) patients were managed with antibiotics only. Repeat abdominal surgery and local drainage were performed in 8.9% vs. 6.6%; $p=0.593$; 2.0% vs. 3.0%; $p=0.697$ for HT and LT, respectively. Overall, 22 (11%) patients presented with pelvic collections (seven (7.1%) patients in the HT group vs. 15 (14.9%) in the LT group; $p=0.079$). The overall rate of permanent stoma was 15.5% with no difference found between both groups ($p=0.303$).

Pathological results. Oncological results are presented in Table III. Median lymph node yield was 18 in both groups ($p=0.720$). No differences were found between both groups in terms of T tumor stage ($p=0.744$). Overall, 28 (14.0%) patients had no residual tumor (pT0 stage), of which 17 received standard neoadjuvant CRT with Xeloda and one short course radiotherapy alone. Nine patients had initial mucosal endoscopic resection and had no residual tumor on the specimen. Adjuvant therapy was performed in 53 (26.5%) patients with no difference found between both groups ($p=0.806$).

Long-term outcome. For all patients, median of follow-up was 38.5 months (range=1-153 months). Overall, 52 (26.0%) patients underwent postoperative chemotherapy with no difference between the two groups ($p=0.806$). Overall recurrence rate affected 39 (19.5%) patients, with no differences found between the two groups ($p=0.343$). Overall survival at 3 and 5 years was 95% and 92.9% without difference between two groups (HT vs. LT; 94.1%/90.1% vs. 97%/92.9% $p=0.640$) (Figure 1). Disease-free survival at 3 and 5 years was 81.5% and 80.5% with no difference between the two groups (HT vs. LT; 84.2%, 83.2% vs. 78.8% 77.8%; $p=0.417$, respectively) (Figure 2). The overall rate of permanent stoma was 12% with no difference found between both groups.

Discussion

This present single-center case series reports that LT ligation of the IMA during surgery for rectal cancer might reduce postoperative severe morbidity rate without compromising oncological results although the extent of surgical resection is less extensive. It is still widely reported, that HT is a condition sine qua non for curative rectal cancer surgery and to create a tension free and safe rectal anastomosis. However, our present study demonstrates that only in a very limited number of patients HT is necessary for safe confection of the anastomosis but with a significant higher rate of severe perioperative complications for such an approach. Another important finding of our present study is the fact, that LT had no impact on the radicality of lymphadenectomy and the oncological outcome.

Severe postoperative complications were significantly less frequent in the LT group compared with the HT group (9% vs. 19%, $p=0.048$). Overall postoperative complications, anastomotic leak, pelvic collection, as well as repeat surgery rates were all, although statistically not significant, lower in LT group compared with HT group. Most published case series, meta-analyses and also a prospective randomized trial did not demonstrate any statistical difference regarding the incidence of anastomotic leak between LT and HT ligation (11, 21-23). Only one recent meta-analysis reported on a significantly lower rate of anastomotic leakage in patients having undergone LT rectal cancer surgery (24). Furthermore, in this meta-analysis, morbidity was also higher in the HT group (OR=1.39; 95%CI=1.05-1.68; $p=0.05$). In our study we selected patients without metastatic disease requiring associated surgical procedures (mainly other organ resections) in order to decreased some confusing variables which could increase anastomotic leak rates or mortality rates (25, 26).

Overall, 3% of LT patients required a secondary HT ligation (transection of LCA) because of insufficient colon length. In all other LT patients (97%), postoperative outcome was not impaired, reflecting a satisfactory anastomosis quality, even when colo-anal anastomosis was required. Laparoscopic rectal resection with LT seems to be associated with an increased conversion rate (28% vs. 17%, $p=0.017$), illustrating a probably more demanding technique. However, other authors have already reported conversion rates ranging between 10% and 31%, so the latter result should be interpreted carefully (27, 28). Anatomic variations related to IMA division branches that have been described by some authors, could play a role in increasing LT technique difficulty, compared with HT ligation (7).

The influence of extensive lymphadenectomy at the root of the IMA remains a matter of debate. Although the presence of positive lymph node yield at the IMA root represents an unfavorable prognostic factor (5, 29) the rate of positive

lymph node at the root of IMA has been reported around 1.7% (5). In the previously mentioned study, out of the 20 patients (from a cohort of 1188 patients) who had at least one positive lymph node at the IMA root, only eight patients (0.7%) had negative lymph nodes below the LCA, *i.e.* skip lymph node metastases, which would be left in case of LT ligation. Current results reveal both similar lymph node yield as well as long-term survival in both LT and HT groups. This is in accordance with results reported by other authors (5, 30). Furthermore, extensive lymphadenectomy associated with HT ligation of IMA has been reported to increase genitourinary dysfunction, when compared with LT ligation (11).

Although our current results are in favor of LT ligation of IMA, they should be interpreted with care and some points need to be underlined. First of all, this study is a retrospective case series over a long time period from 2005 to 2017. The number of patients is too small to find significant differences regarding the impact of LT on local lymphatic tumor recurrence at the root of the IMA, disease-free survival and overall survival compared to extended lymphatic clearance at the root of the IMA during HT. Finally, there is a lack of genito-urinary evaluation in the postoperative period in this present study.

Nevertheless, our study is solid since the included patient population is homogenous (all included patients underwent resection for rectal cancer with no associated complementary resection, and had no synchronous metastases), a high rate of patients underwent neoadjuvant therapy, and a large-number laparoscopic rectal resections were included in the study population

In conclusion, our study findings support previous findings that LT of IMA does not impair long-term oncological outcome and is associated with improved short-term postoperative outcome. More randomized studies are, however, needed to validate these results.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

Authors' Contributions

Study concept and design: Ouaiissi, Nayeri, Iskander; Acquisition of data: Ouaiissi, Nayeri, Iskander, Artus, Michot, olivier Muller; Analysis and interpretation: Ouaiissi, Tabchouri; Drafting the manuscript: Ouaiissi, Tabchouri; Critical review of the manuscript: Bourlier, Pabst-Giger, Kraemer-Bucur, Lecomte, Salame; Statistical analysis: Ouaiissi, Tabchouri; Administrative, technical, and material support: Ouaiissi; Study supervision: Ouaiissi.

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