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ORIGINAL ARTICLE

# High versus low ligation of inferior mesenteric vessels in rectal cancer surgery: A retrospective cohort study

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## Summary

***Purpose:*** *To retrospectively evaluate the short-term and the long-term oncological outcome between two groups of patients who had undergone either high or low ligation of inferior mesenteric vessels (IMV) in rectal cancer surgery.*

***Methods:*** *Between January 2009 and December 2014, 120 patients with rectosigmoid and rectal adenocarcinoma were operated with curative intent as first therapeutic option. Patients were divided in two groups depending on the level of the inferior mesenteric artery (IMA) ligation. High ligation was defined as the division of the IMA less than 2cm from the aorta followed by the ligation of the inferior mesenteric vein at its origin from the lower border of the pancreas (n=76), while low ligation was defined as the division of IMA immediately distal to the origin of the left colic artery (n=44).*

***Results:*** *The median follow up was 51 months. Univariate analyses disclosed that low ligation was related to a higher postoperative complications rate, mainly related to the higher rate of urinary dysfunction but it was also related to a favorable 5-year overall survival (OS) rate. However, multivariate analyses among factors which might influence the short- and long-term outcomes did not disclose the level of ligation as a factor influencing the postoperative course, the recurrence, the disease free survival (DFS) and the 1-, 3- and 5-year OS rates.*

***Conclusions:*** *The present study disclosed no differences in surgical, histological, short-term and long-term oncological outcomes between patients treated with either high or low ligation of IMA.*

***Key words:*** *inferior mesenteric artery, ligation, oncological outcome, postoperative outcome, rectal cancer, recurrence*

## Introduction

Over the previous decades, major changes have been made in the surgical treatment of rectal cancer. The worldwide adoption of the total mesorectal excision [1], the development of sophisticated surgical instruments, the progresses in laparoscopic surgery and the establishment of adjuvant and neoadjuvant treatment options, dramatically changed the outcome of rectal cancer patients.

However, the level of the inferior mesenteric vessels (IMV) ligation, still remains controversial. The inferior mesenteric artery (IMA) can be ligated either directly at its origin from the aorta (high ligation) or just distally to the origin of the left colic artery (low ligation).

Scott-Conner [2] recommends low ligation of the IMA, stating that the risk of poor blood supply to the anastomosis overweights the oncological benefits of performing a high ligation. Similarly, Marcello and Schoetz [3] do not advice high ligation of the IMA as a routine. Cohen [4] also reports

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that the oncologic benefits of the IMA ligation with clearance of the high and periaortic lymph nodes are minimal.

On the other hand, Keighley [5] recommends high ligation in cases of radical surgery and low ligation in palliative procedures. Rullier [6] also advocates the high ligation, reserving the low one in cases of suspected vascular insufficiency of the mid colic artery or for Hartmann's procedure.

The lack of prospective, randomized clinical trials with sufficient follow-up and consistent methodology is responsible for the lack of a consensus [7], leaving enough room for further studies.

In our Department, both high and low ligation are performed for rectosigmoid and rectal cancer surgery and the aim of the present study was to evaluate both the immediate perioperative as well as the long-term oncological outcomes of these two techniques.

## Methods

*Patients*

From 2009 onwards, all patients who were referred to our Department for further investigation and treatment, having been diagnosed with recto-sigmoid and rectal tumors, were prospectively enrolled. Demographics, clinical data, adjuvant or neo-adjuvant therapies, type of operation, postoperative complications, histological findings, follow-up and elapse time to either local or distant recurrence were recorded. The Hospitals' review board approved this study.

All patients suffered from sporading colorectal cancer and all had undergone colonoscopy and biopsies for histological confirmation of the disease. For loco-regional disease staging, they were submitted to magnetic resonance imaging (MRI) of the pelvis.[8] For staging of the metastatic disease, they were submitted at least to computer tomography (CT) of the thorax and abdomen.

Prior to any therapeutic option implementation, all cases were discussed in the Multi-Disciplinary Cancer meeting (which comprised Surgeons, Oncologists, Radiologists and Pathologists). The most suitable therapeutic strategy was planned and was adopted by all surgeons.

Between January 2009 and December 2014, 218 patients with recto-sigmoid and rectal tumors, were referred to our Department. Excluding patients who (i) were diagnosed with histological types others than adenocarcinoma (n=7), (ii) were operated on as an emergency (n=4), (iii) were operated on for palliation (n=24), (iv) were referred for neo-adjuvant chemo- & radio-therapy since their locoregional disease had been clinically staged as T4 or N1b or greater (n=37) [9], (v) were diagnosed as stage IV, even though a curative resection was achieved (n=8) and (vi) suffered from multiple distant metastases (n=18), a total of 120 adenocarcinoma patients were submitted to surgery with curative intent, as first therapeutic option. Those 120 patients constituted the material of the present study and were retrospectively analyzed.

*Surgical technique*

Patients were divided in two groups depending on the level of the IMV ligation. High ligation was defined as the division of the IMA less than 2cm from the aorta followed by the ligation of the inferior mesenteric vein at the lower border of the pancreas. Low ligation was defined as the division of IMA just distally to the origin of the left colic artery.

All patients were operated on electively and all had undergone bowel preparation overnight.

Both the level of IMA ligation, as well as all aspects of the operations were on surgeons' preference. For JG and IK, surgeons with 15 and 13 years surgical experience respectively at the time of the study's closure, the preferable approach was high ligation, while they only exceptionally performed diverted ileostomy in cases of low anterior resection. For EF and EP, surgeons with 22 and 21 years surgical experience respectively at the time of the study's closure, the preferable approach was low ligation, while both of them routinely performed diverted ileostomy in cases of low anterior resection. Obviously, the final decision for high or low ligation of IMA was taken by the surgeons intraoperatively, primarily based on patient's specific anatomical characteristics and intraoperative findings and only secondary to their personal preference.

One hundred eighteen operations were performed through a midline laparotomy. In one patient the abdominal part of an abdominoperineal resection (APR) was attempted laparoscopically, but the method converted to a conventional open approach due to the size (T4) and the length (8cm) of the tumor, and in one patient who underwent APR, the abdominal part of the operation was completed laparoscopically.

The operations performed were: anterior resection and colo-rectal anastomosis (n=43), anterior resection and Hartmann's (n=3), anterior resection with colo-rectal anastomosis and diverted loop ileostomy (n=1), low anterior resection (LAR) and colo-rectal anastomosis (n=26), LAR with colo-rectal anastomosis and diverted loop ileostomy (n=35) and abdomino-perineal resection (APR) (n=12). LAR was defined as any case of colo-rectal anastomosis establishment distally to the *cul-de-sac*.

Excluding the 12 APRs and the 3 Hartmann's procedures, 105 patients underwent anastomosis. Sixty two patients underwent a stapled and 43 a hand-sewed anastomosis.

*Postoperative course*

Postoperative complications were classified according to the Clavien-Dindo classification system [10].

Postoperative paralytic ileus was defined as the necessity for nasogastric drain tube presence beyond the 5$^{th}$ postoperative day.

Urinary dysfunction was defined as either urinary tract infection or the necessity for Folley's catheter reinsertion after its initial withdrawal.

**Table 1.** Clinicopathological characteristics of the enrolled patients

| *Characteristics* | Parameter | *High ligation (n=76) n (%)* | *Low ligation (n=44) n (%)* | *p value* |
|---|---|---|---|---|
| Gender | Male | 39 (51) | 30 (68) | 0.072 |
| | Female | 37 (49) | 14 (32) | |
| Age (years) | Median + IR | 70 (63 - 79) | 72 (64 - 77.75) | NS* |
| ASA score | ASA 1 | 30 (39) | 22 (50) | NS |
| | ASA 2 | 37 (49) | 18 (41) | |
| | ASA 3 | 9 (12) | 4 (9) | |
| Primary tumor | Rectosigmoid – Upper rectum | 37 (49) | 26 (59) | NS |
| | Mid – Lower rectum | 39 (51) | 18 (41) | |
| Type of operation | AR + Anastomosis | 42 (55) | 1 (2) | 0.015 |
| | AR + Hartmann's | 3 (4) | | |
| | AR + Anastomosis + Diverted ileostomy | 1 (1) | | |
| | LAR + Anastomosis | 21 (28) | 5 (11) | |
| | LAR + Anastomosis + Diverted ileostomy | 4 (5) | 31 (70) | |
| | APR | 5 (7) | 7 (16) | |
| Operating time (min) | Mean + SD | 174 ± 37 | 188 ± 41 | NS* |
| Blood loss (mL) | Mean + SD | 121 ± 15 | 110 ± 20 | NS* |
| Hospital stay (days) | Mean + SD | 7.22 ± 2.35 | 8.11 ± 3.43 | NS* |
| Differentiation | Poorly | 16 (21) | 8 (18) | NS |
| | Moderate | 53 (70) | 27 (61) | |
| | Well | 1 (1) | 3 (7) | |
| | N/A | 6 (8) | 6 (14) | |
| Lymph nodes harvested | Mean + SD | 17.80 ± 6.79 | 17.67 ± 7.28 | NS* |
| T stage | Tis | 6 (8) | 5 (11) | NS |
| | T1 | 10 (13) | 3 (7) | |
| | T2 | 13 (17) | 8 (18) | |
| | T3 | 42 (55) | 25 (57) | |
| | T4 | 5 (7) | 3 (7) | |
| N stage | N0 | 53 (70) | 31 (70) | NS |
| | N1 | 14 (18) | 9 (20) | |
| | N2 | 9 (12) | 4 (10) | |
| TNM stage | 0 | 6 (8) | 5 (11) | NS |
| | I | 17 (22) | 9 (20) | |
| | IIa | 25 (33) | 15 (34) | |
| | IIb | 1 (1) | | |
| | IIc | 1 (1) | 1 (2) | |
| | IIIa | 6 (8) | 1 (2) | |
| | IIIb | 18 (24) | 9 (20) | |
| | IIIc | 2 (3) | 4 (9) | |
| Mucin | Absent | 62 (82) | 35 (80) | NS |
| | Present | 14 (18) | 9 (20) | |
| Lymphatic invasion | Absent | 70 (92) | 40 (91) | NS |
| | Present | 6 (8) | 4 (9) | |
| Perineural invasion | Absent | 72 (95) | 43 (98) | NS |
| | Present | 4 (5) | 1 (2) | |
| Vascular invasion | Absent | 58 (76) | 39 (89) | NS |
| | Present | 18 (24) | 5 (11) | |

ASA: American Society of Anesthesiology, AR: Anterior resection, LAR: Low anterior resection, APR: Abdomino-perineal resection, SD: Standard deviation, NS: Not significant, p=chi square except *Mann- Whitney U test

Only the clinical anastomotic leaks were encountered in the present study. The diagnosis was suspected by patient's symptoms and clinical examination's signs, was established by abdominal CT scan and either reoperation or interventional radiology was required for their treatment.

Postoperative bleeding was defined as either intraperitoneal accumulation of blood or gastrointestinal tract bleeding requiring hypovolemic shock treatment, blood products transfusion and/or reoperation for its treatment.

*Oncological outcome*

The pathological stage of the disease was based on the 7th TNM Classification [11]. During follow-up, the elapse period since the initial operation for recurrence development, the site and the organ of recurrence, the therapeutic strategies and the final outcome were documented, in order to be estimated the DFS and OS.

*Statistics*

All statistical calculations were performed with the use of the R software for Windows, version 3.3.2. The data were entered into Microsoft excel sheet and imported to R. Chi-square was used for categorical data analysis. Mann-Whitney U test was used for the statistical analyses of quantitative data. A p value <0.05 was considered as statistically significant. DFS and OS were calculated for all patients and Kaplan–Meier curves were generated. The significance of survival difference was estimated by log-rank test. Multivariate analysis of the factors that might influence the recurrence, DFS and OS was carried out using the Cox proportional-hazards model.

## Results

The clinicopathological characteristics of the patients enrolled are presented in Table 1. There were 76 patients in the high ligation and 44 patients in the low ligation group. The higher incidence of the male patients in the low ligation group as well as the discrepancies in the type of the operations performed could be explained by the retrospective nature of the study.

*30-days postoperative morbidity* (Table 2)

Five out of the 76 patients in the high ligation group developed 5 complications (6.5%) and 8 patients out of the 44 in the low ligation group de-

**Table 2.** 30-days postoperative morbidity and mortality

| *Complication* | | *High ligation* | *Low ligation* | *p value* |
|---|---|---|---|---|
| *Clavien-Dindo* | Type of complication | *(n=76)* *n (%)* | *(n=44)* *n (%)* | |
| II | Ileus | 2 (3) | 3 (7) | NS |
| II | Urinary dysfunction | | 6 (14) | 0.0008 |
| III | Anastomotic leakage | 1 (1) | 2 (5) | NS |
| III | Postoperative bleeding | 2 (3) | | NS |
| | Overall | 5 (6.5) | 11(25) | 0.003 |
| V | Deaths | 2 (3) | 2 (5) | NS |

NS: non significant

**Table 3.** Multivariate analysis among factors which might influence postoperative morbidity

| *Parameter* | *RR* | *p value* | *95% confidence interval* | |
|---|---|---|---|---|
| High or low ligation | 1.543692 | 0.125616 | -0.02945 | 0.236681 |
| Age | 1.855378 | 0.066295 | -0.0004 | 0.012201 |
| Gender | 0.545263 | 0.586708 | -0.09869 | 0.173571 |
| ASA score | -0.83945 | 0.403086 | -0.13884 | 0.056234 |
| Type of anastomosis | 0.705421 | 0.482081 | -0.05744 | 0.120911 |
| Stage | 0.53002 | 0.597196 | -0.04065 | 0.070314 |
| Grade | -1.25684 | 0.21155 | -0.15113 | 0.033852 |
| Lymph node infiltrated | 0.347594 | 0.728828 | -0.15517 | 0.22115 |
| Perineural inasion | -0.61522 | 0.539716 | -0.44642 | 0.234961 |
| Vascular invasion | -0.77588 | 0.439533 | -0.25254 | 0.110465 |
| Lymphatic invasion | -0.85008 | 0.397177 | -0.35307 | 0.141145 |
| Mucin presence | 0.300578 | 0.76432 | -0.14464 | 0.196346 |

RR: relative risk

veloped 11 complications (25%) and this difference was statistically significant (p=0.003). Five patients developed postoperative paralytic ileus, which in all cases was treated conservatively. Six patients (14%) in the low ligation group developed urinary dysfunction, namely lower urinary tract infection (n=3) and urinary retention (n=3) and this difference was statistically significant (p=0.0008). Two patients in the high ligation group developed intraperitoneal (n=1) and upper GI tract (n=1) bleeding, which both were managed conservatively. One patient in the high and two patients in the low ligation group developed anastomotic leakages. All leakages occurred in patients who had undergone ultralow anterior resection with stapled colo-colonic anastomosis and prophylactic loop diverted ileostomy. In one patient, the presacral collection was drained percutaneously, while for the remaining two patients because they developed signs of acute abdomen and sepsis, a reoperation was required. Multivariate analysis (Table 3) among factors which might affect patients' postoperative course, disclosed advanced age as a marginally statistically significant factor (p=0.066) but did not disclose the level of ligation as a predisposing factor for postoperative morbidity.

*30-days postoperative mortality*

Among the 4 deaths (2 in the high ligation and 2 in the low ligation group), only one was directly related to the procedures as a consequence of anastomotic leak in the low ligation group. The remaining 3 deaths occurred as result of severe respiratory failure (Table 2).

*Lymph nodes status*

There were no significant differences between the two groups in the mean numbers of either the harvested (17.80 vs 17.67) or the metastatically infiltrated lymph nodes (1.1 vs 1.3) (Table 1).

*Recurrence*

Excluding the 4 patients who died postoperatively, 13 out of the 116 remaining patients (74 in the high ligation and 42 in the low ligation group), developed recurrence (11.2%) (Table 4). The overall recurrence rate was 12% in the high ligation and

**Table 4.** Oncological outcome

| *Oncological outcome* | *High ligation (n=74) n (%)* | *Low ligation (n=42) n (%)* | *p value* |
|---|---|---|---|
| Recurrence Overall | 9 (12) | 4 (9.5) | NS |
| Local | 3 (4) | 3 (7) | NS |
| Distant | 6 (8) | 1 (2) | NS |

NS: non significant

**Table 5.** Characteristics of recurrences

| *Gender* | *Age (years)* | *Type of operation* | *Type of ligation* | *Time for recurrence (months)* | *Differentiation* | *Stage* | *Recurrences* |
|---|---|---|---|---|---|---|---|
| M | 81 | APR | Low | 6 | Poorly | T4N2 | Local |
| F | 69 | AR | High | 13 | Poorly | T3N2 | Local |
| M | 65 | AR | High | 13 | Poorly | T3N2 | Liver |
| F | 64 | APR | Low | 18 | Poorly | T4N1 | Local |
| M | 62 | AR | High | 22 | Poorly | T2N0 | Lung |
| F | 81 | AR | High | 23 | Moderate | T3N0 | Liver |
| M | 49 | LAR | Low | 27 | Moderate | T3N2 | Local |
| M | 78 | LAR | High | 28 | Moderate | T3N2 | Peritoneal |
| M | 67 | APR | High | 30 | - | T3N2 | Lung |
| M | 54 | APR | High | 35 | Moderate | T4N1 | Local |
| M | 55 | APR | High | 37 | Moderate | T3N0 | Local |
| M | 50 | LAR | Low | 50 | Poorly | T3N0 | Liver |
| F | 89 | APR | High | 59 | Poorly | T3N1 | Lung |

M: male, F: female, AR: Anterior resection, APR: Abdominoperineal resection, LAR: Low anterior resection

9.5% in the low ligation group. Local recurrences developed in 6 patients (5%); 3 (4%) in the high ligation and 3 (7%) in the low ligation group. Distant recurrences developed in 7 patients (6%); 6 in the high ligation (8%) and one (2%) in the low ligation group. Three patients developed liver metastases, 3 lung metastases and one peritoneal carcinomatosis (Table 5). Multivariate analyses among factors which might influence the recurrence, did not disclose the level of ligation as related to that (Table 6).

*Disease free survival*

All postoperatively surviving patients (n=116), were enrolled for DFS calculation. Within a median follow up period of 48 months, the univariate analysis did not conclude in any statistically significance difference between the level of ligation and the DFS. However, multivariate analysis among factors which might influence the DFS (Table 7) disclosed recurrence (p<0.001), advanced age (p=0.002), perineural invasion (p=0.03) and vascular invasion (p=0.02) as independent dismal prognostic factors. The level of ligation was not found as related to the DFS. The survival curves for the DFS between the two groups of patients are presented in Figure 1A.

*Overall survival*

During a median follow up period of 51 months, none of the patients was lost during the follow up, while 12 patients died from causes unrelated to the rectal cancer. There were 3 deaths related to the rectal cancer within 12 months from the initial operation; thus the 1-year OS was calculated in 113 patients, the 2-year OS in 110, the 3-years OS in 88, the 4-year OS in 62, and the 5-year OS in

**Table 6.** Multivariate analysis among factors which might influence recurrence

| *Parameter* | *RR* | *p value* | *95% confidence interval* | |
|---|---|---|---|---|
| High or low ligation | -0.38658 | 0.699861 | -0.13808 | 0.09303 |
| Gender | -0.00612 | 0.995126 | -0.12049 | 0.119747 |
| Age | -0.60021 | 0.549685 | -0.00731 | 0.003911 |
| Stage | 0.371692 | 0.710886 | -0.04704 | 0.068735 |
| Grade | **-3.35332** | **0.001118** | **-0.23112** | **-0.05934** |
| T stage | **2.320442** | **0.022288** | **0.01243** | **0.158661** |
| Lymph node harvested | -0.0816 | 0.935124 | -0.00839 | 0.00773 |
| Lymph node infiltrated | 0.614848 | 0.540011 | -0.11601 | 0.220266 |
| Perineural invasion | **-2.50754** | **0.013719** | **-0.66914** | **-0.07812** |
| Vascular invasion | 1.173019 | 0.243494 | -0.0641 | 0.249717 |
| Lymphatic invasion | 0.273526 | 0.784997 | -0.18339 | 0.242062 |
| Mucin presence | 0.446958 | 0.655844 | -0.11645 | 0.184208 |

Bold numbers denote statistical significance

**Table 7.** Multivariate analysis among factors which might influence the DFS

| *Parameter* | *RR* | *p value* | *95% confidence interval* | |
|---|---|---|---|---|
| Recurrence | -3.69827 | 0.000352 | -40.3027 | -12.1635 |
| High or Low ligation | 1.630783 | 0.10602 | -1.48051 | 15.17091 |
| Gender | -0.80955 | 0.420082 | -12.178 | 5.11852 |
| Age | -3.07073 | 0.002737 | -1.03064 | -0.2217 |
| Stage | -1.6685 | 0.098284 | -7.67867 | 0.662315 |
| Grade | 0.660737 | 0.510271 | -4.34333 | 8.682442 |
| T stage | 0.182693 | 0.855401 | -4.90261 | 5.897354 |
| Lymph node harvested | -0.65263 | 0.515462 | -0.7714 | 0.389445 |
| Lymph node infiltrated | 0.807406 | 0.421312 | -7.19109 | 17.0647 |
| Perineural invasion | **-2.12785** | **0.03576** | **-45.4266** | **-1.59495** |
| Vascular invasion | **2.224153** | **0.028342** | **1.379824** | **24.12474** |
| Lymphatic invasion | -0.20255 | 0.839888 | -16.8858 | 13.75662 |
| Mucin presence | -0.2099 | 0.834164 | -11.9804 | 9.69 |

Bold numbers denote statistical significance

**Table 8.** Overall survival

| | *n* | *High ligation n (%)* | *Low ligation n (%)* | *p value* |
|---|---|---|---|---|
| Patients enrolled in follow up | 116 | 74 | 42 | |
| 1-year survival | 113 | 73 (98.5) | 40 (95.2) | NS |
| 2-year survival | 110 | 72 (97.3) | 38 (90.5) | NS |
| 3-year survival | 88 | 54 (73) | 34 (81) | NS |
| 4-year survival | 62 | 36 (48.5) | 26 (62) | NS |
| 5-year survival | 45 | 22 (30) | 23 (55) | 0.007 |

NS: non significant

**Table 9.** Multivariate analysis among factors which might influence the 1-year survival

| *Parameter* | *RR* | *p value* | *95% confidence interval* | |
|---|---|---|---|---|
| **DFS** | **45.54578** | **<0.0001** | **0.963773** | **1.051596** |
| **Recurrence** | **12.68701** | **<0.0001** | **18.62694** | **25.53563** |
| High or Low ligation | -0.52266 | 0.602405 | -2.322 | 1.353969 |
| Age | -0.61402 | 0.540642 | -0.11611 | 0.061243 |
| Gender | 0.85055 | 0.397114 | -1.02236 | 2.555758 |
| Grade | 1.207438 | 0.230199 | -0.53941 | 2.21525 |
| T stage | 0.660069 | 0.510774 | -0.85424 | 1.705575 |
| N stage | **3.95137** | **0.000148** | **5.068559** | **15.29886** |
| TNM stage | -1.83188 | 0.070038 | -2.47122 | 0.098963 |
| Lymph node harvested | 0.654284 | 0.514477 | -0.08218 | 0.163009 |
| **Lymph node infiltrated** | **-5.39681** | **<0.0001** | **-3.44272** | **-1.59139** |
| Mucin presence | -0.53737 | 0.592244 | -2.74355 | 1.574442 |
| Lymphatic invasion | -0.30243 | 0.76297 | -3.69089 | 2.714791 |
| Perineural invasion | 0.643437 | 0.521459 | -3.07472 | 6.024698 |
| **Vascular invasion** | **-2.76531** | **0.006808** | **-5.96143** | **-0.97966** |

Bold lettering and numbers denote statistical significance

**Table 10.** Multivariate analysis among factors which might influence the 3-year survival

| *Parameter* | *RR* | *p value* | *95% confidence interval* | |
|---|---|---|---|---|
| **DFS** | **37.44305** | **<0.0001** | **0.927045** | **1.031256** |
| **Recurrence** | **13.98776** | **<0.0001** | **23.09157** | **30.76312** |
| High or Low ligation | -0.19185 | 0.848389 | -2.09501 | 1.727017 |
| Age | 0.084046 | 0.933247 | -0.08694 | 0.094599 |
| Gender | 0.486816 | 0.627828 | -1.39388 | 2.295187 |
| Grade | 1.858707 | 0.067045 | -0.09418 | 2.710102 |
| **T stage** | **0.351642** | **0.726106** | **-1.15813** | **1.6545** |
| **N stage** | **2.195307** | **0.031278** | **0.748291** | **15.45513** |
| TNM stage | -2.19654 | 0.031186 | -3.05529 | -0.14878 |
| Lymph node harvested | 0.627556 | 0.532226 | -0.08442 | 0.162038 |
| Lymph node infiltrated | -0.60924 | 0.544234 | -2.51362 | 1.336435 |
| Mucin presence | -0.86609 | 0.389242 | -3.45869 | 1.362912 |
| Lymphatic invasion | 0.464007 | 0.644005 | -3.17819 | 5.107748 |
| Perineural invasion | 0.481022 | 0.63192 | -4.13451 | 6.76602 |
| Vascular invasion | -1.72586 | 0.088547 | -4.87319 | 0.349508 |

Bold lettering and numbers denote statistical significance

45 (Table 8). Univariate analysis disclosed that patients who had undergone low ligation had better 5-year OS (p=0.007). Following that, multivariate analysis among factors which might influence the 1-, 3- and 5-year OS, was performed and the results are presented in Tables 9, 10 and 11. In none of them the level of ligation was found as related to the OS. The survival curves for the OS between the two groups of patients are presented in Figure 1B.

## Discussion

The present study is characterized by severe limitations such as its retrospective nature, the small number of the enrolled patients and the non-homogeneous population of them as well as the most recognizable bias in scientific surgery; the role, the skills, the experience, the preferable technique and the personal decision-making preferences of every single surgeon who enrolled patients. Thus, in the evidence-based medicine era, its results, in the best case scenario, cannot rich a level of evidence higher than 3b.

However, it attempted to investigate a debatable, for more than a century, subject in the rectal cancer surgery: the significance (if any) of the "high" or the "low" ligation of the IMV, both in the early postoperative as well as in the long-term on-

**Table 11.** Multivariate analysis among factors which might influence the 5-year survival

| *Parameter* | *RR* | *p value* | *95% confidence interval* | |
|---|---|---|---|---|
| **DFS** | **11.04222** | **<0.0001** | **0.683522** | **0.995515** |
| **Recurrence** | **5.765247** | **<0.0001** | **14.12759** | **29.73985** |
| High or Low ligation | -1.44412 | 0.160211 | -6.26605 | 1.089249 |
| Age | 0.656848 | 0.516839 | -0.12024 | 0.233471 |
| Gender | -0.48405 | 0.632255 | -4.4871 | 2.774109 |
| **Grade** | **2.906364** | **0.007219** | **1.17157** | **6.797709** |
| T stage | 0.150812 | 0.881245 | -2.87284 | 3.328659 |
| **N stage** | **2.7833** | **0.009704** | **5.868772** | **38.79352** |
| **TNM stage** | **-2.65561** | **0.01312** | **-7.16155** | **-0.91854** |
| Lymph node harvested | 1.27501 | 0.213169 | -0.10551 | 0.45184 |
| Lymph node infiltrated | -1.4851 | 0.149099 | -7.65386 | 1.226386 |
| Mucin presence | -1.1837 | 0.246849 | -8.29369 | 2.225291 |
| Lymphatic invasion | 1.313669 | 0.200011 | -2.64565 | 12.0623 |
| Perineural invasion | 0.65535 | 0.538693 | -5.15431 | 7.28602 |
| Vascular invasion | -1.42569 | 0.107458 | -8.36057 | 1.505341 |

Bold lettering and numbers denote statistical significance

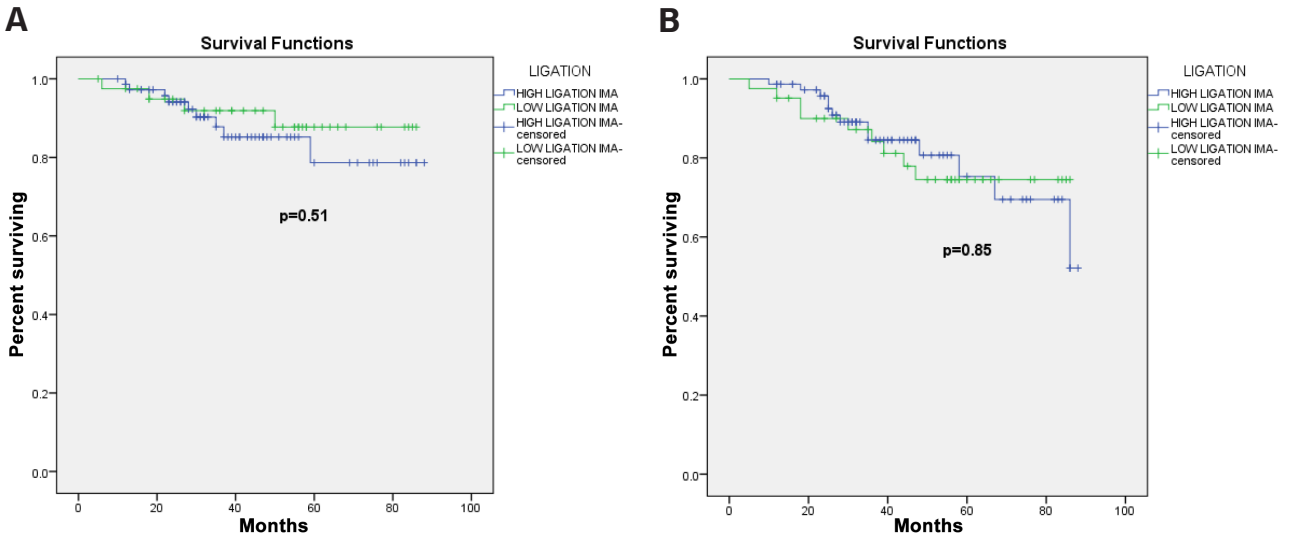


**Figure 1. (A)** Kaplan-Meier survival curves for disease free survival between the two groups of the study. **(B)** Kaplan-Meier survival curves for overall survival between the two groups of the study.

cological outcome. By using multiple multivariate analyses among several factors which have been proposed as related to the outcomes, it concluded that the level of ligation was not independently related either to the short- or the long-term outcome of rectal cancer surgery.

Authors favoring the high ligation technique emphasize that it allows the *en bloc* dissection of the lymph nodes at and around the origin of the IMA [12], a fact possibly contributing to a more accurate tumor staging [13], it enables easy creation of mesenteric window and easily entrance into the pelvis both in open and laparoscopic surgery [14], and it enables the creation of a tension-free anastomosis in the pelvis in cases of low anterior resection [15].

On the other hand, authors favoring low ligation technique emphasize that it allows adequate blood supply to the colon proximal to the anastomoses in cases of low anterior resection, a fact possibly influencing anastomotic leak rate [15]. The fact is that although approximately one fifth of the patients experienced significant blood flow reduction after IMA clamping [16], ischaemia-related anastomotic complications were encountered in less than 2% of the cases [17], mainly affecting patients of advanced age, with cardiovascular and cerebrovascular disease as well as hypertension [17,18]. Thus, several studies [19-21] supported that high ligation did not increase the risk of anastomotic leak.

High ligation technique has also been proposed as a safe option for avoiding damage to the autonomic nerves [22], preserving the sexual and urinary function for the majority of the patients [23,24]. Till now, there is not sufficient evidence to support that low ligation offers a better postoperative outcome in terms of sexual and urinary function [25].

In the present study, the 30-day postoperative morbidity was 6.5% for the high and 25% for the low ligation group of patients and this statistically significant difference was mainly related to the urinary complications which were noticed only in the low ligation group. There was no difference either in the incidence of anastomotic leaks (1 vs 5%, respectively) or in the incidence of postoperative mortality (2 vs 5%, respectively). Among the 4 in-hospital deaths, only one was directly related to anastomotic leak in the low ligation group of patients. Multivariate analysis did not disclose the level of ligation as an independent factor affecting the early postoperative course.

Although previous studies [12,13,26] suggested that high ligation of IMA significantly increased the number of lymph nodes harvested, facilitating a more accurate tumor staging, randomized control trials [21,27] confirmed no significant differences in the number of lymph nodes yield between the two groups. Meanwhile, the metastatic infiltration of the regional lymph nodes represents the most significant independent dismal prognostic factor for colorectal cancer patients [28,29]. However, the American Society of Clinical Oncology, the National Comprehensive Cancer Network and the United Kingdom Royal College of Pathologists take under consideration only the total number but not the location of the positive lymph nodes, stipulating a minimum of 12 lymph nodes yield per case as the minimum necessary for accurate tumor staging [30].

The present study, disclosed that the mean number of lymph nodes harvested was practically identical between the two groups of patients (17.80 for the high ligation and 17.67 for the low ligation). The larger, than the proposed by the recommendations, mean number of the harvested lymph nodes detected in both groups, probably reflects the higher level of awareness among pathologists nowadays, for the crucial role of careful lymph node detection in the specimen [31] .

High ligation technique allows the dissection of the lymph nodes at the origin of the IMA. Although several studies [32-34] agreed that metastatic deposits at the root of the IMA occur in less than 5% of the patients and rarely upstage the disease due to cancerous involvement of these proximal nodes [35], the prognostic significance of these apical-node metastasis remains unclear. Yi et al. [36] reported that apical-node metastasis is not a poor prognostic factor for stage III sigmoid colon or rectal cancer after high ligation. On the other hand, Peng et al. [37] reported that apical node metastasis represents an important prognostic factor for node-positive rectal cancer patients, providing additional survival-related prognostic classification irrespectively to the N stage.

In the present study, the significance of the apical lymph node(s) positivity in the high ligation group was not investigated, because we followed the 7th TMN classification,[11] in which only the total number of positive lymph nodes was encountered.

Current literature reveals that the local recurrence rate in rectal cancer patients has been decreased down to 5-10% [38,39].

The present study confirmed a similar local recurrence rate (6 out of 116, 5%), without significant difference between the high ligation and the low ligation group of patients. However, 5 out of the 6 locally recurred patients had been pathologically staged as IIIb and IIIc, thus somebody could specu-

late that these patients should had been referred for neo-adjuvant chemo- and radio-therapy. The answer is that the patients were referred for neo-adjuvant therapies according to the preoperative clinical stage of the disease, based on the pelvic MRI findings. Since the sensitivity of MRI does not exceed 86% for the T-stage and 85% for the N-stage [40] , obviously some patients were under-staged clinically.

It is known that the older rectal cancer patients have worst OS compared to the younger ones, although their death is not associated with the disease, while young patients have a lower hazard of dying [41,42]. Moreover, local recurrence [43-45] and metastatic disease development [46] are independently related to a poorer prognosis. However, randomized control trials [21,27], systematic reviews [7,47,48] and a meta-analysis [49] failed to demonstrate any long-term survival benefit for rectal cancer patients treated with high ligation, compared to those treated with low ligation. Only the meta-analysis published by Chen et al. [50] disclosed a better 5-year OS in the high ligation group of patients. However, Chen's meta-analysis enrolled only studies published in Chinese, thus excluded from Cirocchi's meta-analysis due to language restriction.

The present study failed to demonstrate the level of ligation as a factor affecting either the DFS or the 1-, 3- and 5-year OS of the rectal cancer patients.

## Conclusion

Despite its limitations (retrospective in nature, small number of enrolled patients, bias in the terms of the surgical skills or the preferable technique used by every single surgeon who enrolled patients), the present study did not disclose significant differences in the surgical, histological, short-term and long-term oncological outcome in patients with rectosigmoid and rectal cancer who were treated with either high or low ligation of the inferior mesenteric vessels. The necessity for a randomized trial on that subject remains mandatory.

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## Conflict of interests

The authors declare no conflict of interests.

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